THE STRUCTURAL AND FUNCTIONAL PLASTICITY OF INFLUENZA VIRUS*

WILSON SMITH
M.D. Manc., F.R.S.
ESSOR OF BACTERIOLOGY IN THE UNIVERSITY OF LONDON,
AT UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL

HE science of virology is essentially a child of the ant century. As recently as 20 years ago relatively viruses had been isolated, and though a considerable unt of knowledge had been gained concerning their iological effects very much less was known about the ase agents themselves: what they are, how they are structed, how they reproduce themselves, and by it mechanisms they exert their noxious influence n the host's economy. In consequence undue hasis was laid upon the few general characteristics h had been firmly established, such as the minute s of the viruses, their filterability and their obligate acellular parasitism. These attributes, taken in unction, were held to connote extreme simplicity of cture and a lack of any means for independent tional activity.

ccessful immunisation against a few infections, like llpox, had, however, long been practised, and the e of extending this method of control to many other s diseases received great encouragement from the recent triumph of Laidlaw and Dunkin in connection dog distemper. It is therefore perhaps not to be dered at that the isolation of an influenza virus from an cases in 1933 raised confident expectations that quest of this scourge was now in sight (Smith et al. 3). With the causative virus in hand and with a nique available for its propagation in laboratory nals, what was to prevent the manufacture of a virus cine for the wholesale immunisation of populations isk? The research of the last two decades has shown ill founded was this early hope, for gradually there come the realisation that influenza is caused not by ingle virus but by several possessing distinctive racteristics. These, moreover, far from being stable ties with predictable behaviour, are plastic organisms ergoing constant changes of structure to produce er forms with changed antigenic constitution, dified architecture and different biological behaviour.

ANTIGENIC PLASTICITY

he first intimation that influenza virus strains ted at different times and in different localities might e important differences of constitution came when ill and Francis (1936) reported the results of compari- based upon serum neutralisation tests in mice. ir claims were soon confirmed both in this country Australia. In 1938 my colleague Dr. Andrewes and blished the results of an antigenic analysis of all the ins then available to us, 28 in number, which had isolated in several different countries (Smith and drewes 1938). It appeared that all the strains were ted to each other through the possession of common igens. There were, however, different degrees of tionship depending upon relative proportions of the ious antigens. The important point was that appar- y there were a limited number of antigenic com- ents and that some strains, our so-called master ins, possessed all the components in significant unts and might therefore be expected to serve as sfactory material for prophylactic immunisation of . At the time this discovery of antigenic diversity ngst influenza virus strains was rather welcomed, because it seemed to provide a plausible explanation of certain epidemiological puzzles and to account for the disappointing results of early field trials of virus vaccines. Then in 1940 came news of influenza virus diversity of an entirely different kind (Francis 1940). A virus was isolated from a perfectly typical case of influenza which was found to have no detectable antigenic relationship whatever with any previously isolated strain. Yet it had all the biological attributes characteristic of an influenza virus, such as infectivity for ferrets and adaptability to mice. The influenza viruses now had to be classified into two major types A and B, and it was not long before the isolation and analysis of more B strains showed that type B, just like type A, comprised a heterogeneous group of related but distinguishable strains. Recent evidence indicates that there may be a third unrelated type C in existence (Taylor 1949).

Most of the A strains isolated up to 1935 were very closely related to the original 1933 virus, labelled W.S. Between 1935 and 1947 new strains showed less affinity with W.S. and more with a standard 1934 virus called PR8. In 1946 a strain isolated in Australia was the precursor of yet another change in the antigenic make-up of current influenza A viruses; thereafter they showed such slight relationship with standard A viruses, in comparison with the close relationships existing amongst themselves, that they demanded classification in a subgroup of type A called A-prime. A-prime viruses have remained dominant throughout the world up to the present time, but the 1949 strains were distinguishable from 1947 strains and those of 1951 showed still further deviation from the original A prime virus.

It is thus abundantly clear that our early conception of a few stable antigenic types, developed possibly by the process of sudden chance mutations, was erroneous. Instead, one now recognises a constant evolution of new antigenic types which replace the older types from which they are derived. Our studies at University College Hospital Medical School have not been concerned primarily with antigenic variation, but from our investigations of a few 1951 strains I think there are clear indications that the development of further types with altered biological behaviour may be imminent.

It is significant for what I shall have to say later concerning the mechanism of variation that antigenic changes occur with great frequency during the course of laboratory adaptations of viruses to new host species. Hirst (1947) for example demonstrated that the passage through mice of two immunologically identical strains resulted in their antigenic deviation, so that the two derivative mouse strains were antigenically distinct not only from each other but also from the parent viruses. It is important to realise, however, that such antigenic modification does not necessarily always accompany mouse adaptation. Sugg (1949) reported adaptation of a virus which resulted in greatly enhanced mouse virulence without any detectable antigenic change.

Whatever the mechanism underlying such antigenic modifications may be, there can be no doubt that the phenomenon is one which usually affects biological behaviour and is of great practical importance. It is probably one of the chief mechanisms by which influenza viruses maintain themselves as human parasites in spite of the constant building up of herd immunity as a result of recurring epidemics. Experience both with cross-immunity experiments in laboratory animals and with field trials of influenza virus vaccines fully confirms what one would expect from established immunological principles—namely, that the immunity response is strictly specific for the particular antigens contained in the infecting virus or the vaccine. Thus in ferrets or mice there is no demonstrable cross protection whatever between virus types A and B, whilst with substrains of

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dney Ringer lecture delivered at University College on March 13, 1952.

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one of the major types the degree of cross protection is proportional to the closeness of antigenic relationship. Also in 1943–44 large-scale field trials in U.S.A. provided conclusive evidence that vaccinated groups of human beings were less susceptible than unvaccinated groups to infection during a subsequent epidemic caused by viruses of the same type as those used for making the vaccine, whereas in 1947 the same vaccine was not effective because the subsequent epidemic was caused by an antigenically distinct strain (Salk et al. 1945, Rasmussen et al. 1947, Francis et al. 1947). Because of this there are some workers who think that the best hope of protecting against a possible recurrence of a devastating pandemic of influenza is to attempt to catch up, as it were, with the antigenic vagaries of the influenza viruses by obtaining the earliest possible information of the emergence of new types so as to incorporate them in a vaccine. Obviously this is a gamble. It is a gamble which is worth taking in our present impotent state, but one in which I think the odds are pretty heavily weighted against us. Whatever the outcome of this line of attack may be there can be no doubt that the study of antigenic relationships is necessary for the elucidation of the epidemiological patterns of epidemics, and much very valuable work in this connection is being carried out under the auspices of the World Health Organisation.

FUNCTIONAL PLASTICITY INDEPENDENT OF ANTIGENIC VARIATION

Whilst fully recognising the great importance of antigenic variation and its significance in many of the phenomena of infection and host resistance, I believe that the antigenic complexities of the influenza viruses have dominated the ideas of research-workers over the last two decades to an unwarranted extent. There are many biological activities of the influenza viruses which vary from strain to strain, or even from time to time with the same strain, which cannot be related to specific antigenic constitutions; for they may change without any associated antigenic modification which can be detected by the numerous techniques available.

The most important attributes of an influenza virus from the human point of view are its communicability and its virulence. The crux of the problem of influenza control lies in the factors which determine the extreme virulence of a pandemic virus such as that which swept over the whole world in 1918–19. It may be found eventually that this characteristic depends upon virulence antigens which at present are unrecognised; but there are good reasons for thinking that factors other than antigenic mutation may be responsible. It is significant that A and B viruses, in spite of their completely different antigenic constitutions, produce attacks of influenza which are clinically quite indistinguishable. On the other hand antigenically indistinguishable strains may display very different degrees of infectivity and virulence. Only last year the Liverpool type virus caused severe influenza with relatively high mortality in the Liverpool area, but typically mild influenza with very low mortality elsewhere. Such virulence differences often become manifest in the course of laboratory investigations. Every influenza virus research-worker is aware of the tendency for viruses to increase in virulence for a new-host species on long-continued passage—a change which cannot be related to mere speed or abundance of virus multiplication and which may, or may not, be associated with antigenic variation. Workers are also well familiar with the different behaviour of strains isolated from the same localised outbreak in respect of the ease with which they can be isolated and their readiness to adapt to various laboratory animals.

THE UNIQUE BEHAVIOUR OF STRAIN HAL

One of the most striking instances of anomalous behaviour is provided by a virus which we isolated during the 1951 epidemic (Smith et al. 1951b). It was one strains isolated within a fortnight and three of came from cases within our own medical schoo hospital. We cannot claim that the four st absolutely identical antigenically, because we ha carried out exhaustive cross-immunity tests; bu antigenic differences there may be are certainly of minor character. Yet one of them, HAL, displayed the outset characteristics which make it unique known strains. The standard technique of virus is now inoculation of material into the amniotic c of the embryonated egg, followed by serial intra-am passage. No strain previously isolated and maint by this technique has killed the chick embryo with production of detectable lesions in organs other the lungs. HAL almost from the outset proved leth the chick embryo and caused widespread lesions invo most organs and tissues of the body. At the amniotic passage six out of seven embryos died, thereafter there was consistently a mortality of clo 100%. The appearances of the brain and meni suggested that this virus strain might possibly neurotropic properties, and this we were able to con by a series of titrations of various organs of the c embryo coupled with histological studies. Whe remind you that the only previous evidence of pos neurotropism of influenza viruses comes from tw three laboratory strains specially adapted to m brain, and considered to be due to chance mutation o excessively rare type, you will appreciate the import of such behaviour on the part of a virus freshly isol from a typical case of influenza in man.

One of the most fascinating problems urge demanding solution is the mechanism by which biological properties of this kind are acquired by a v as it is transmitted from host to host in Nature. This problem which pertains not only to influenza but to many other virus infections of man and lower anim

Any change of biological behaviour must reflect s sort of change in the virus itself; for it is surely evident that absolutely identical organisms must beh under all circumstances in exactly the same way. therefore functional changes can occur without antige change, the viruses must be subject to other type structural modification which help to determine t biological activities. Viruses, of course, are not comp exclusively of antigenic material; indeed there is virus—namely, the grey-lung virus of mice—wh entirely fails to stimulate the production of spec antibodies when inoculated into laboratory animals. would expect therefore both qualitative and quantitat alterations in non-antigenic components to contribute the functional variability of the influenza viruses. Pr tically nothing is known, however, about constitutic modifications of this type, though I think it is a fiel investigation worthy of exploration. On the other h there is a good deal of evidence to indicate that struct changes quite independent of any alterations in nature or quantities of virus constituents may extremely important. For this type of change I prop to use the term "architectural modification." It is architecture of the influenza viruses, involving both th surface configuration and their deeper structure, wh has been our chief interest during the last few ye and which we hope to explore much more fully future.

INFLUENZA VIRUS HÆMAGGLUTINATION

At this point I must outline the elementary fact influenza virus hæmagglutination (Hirst 1941, McClell and Hare 1941) for the benefit of those who are conversant with them. Without a clear mental pic of the basic reactions involved the experiments I wish discuss would appear meaningless.

influenza virus is added to a suspension of the corpuscles of man or fowls the cells aggregate umps which rapidly fall to the bottom of the here they form a characteristic pattern. With e concentrations of the reagents all the virus is down with the cells, so that the clear supernatant found to be non-infective. This is due to a union n virus and cell surface. The virus particles act ks or bridges between the cells binding them er in lattice formation. The surface groups which gether are known as the virus receptors and the ll receptors respectively. If now the agglutinated re centrifuged out of suspension, resuspended in and kept at 37°C virus elution occurs: the virus es itself from the cells to become free again in the ding fluid. Throughout the cycle of hæmagglutina- nd elution the virus remains unchanged, for it is lly infective and can be used over and over again lutinate fresh batches of red blood corpuscles. The scles, however, are permanently altered, for after elution has occurred they are no longer agglutinable esh virus. Virus rendered non-infective by heat nent can likewise agglutinate red cells, but in this he linkage is permanent. The second stage of elution not occur. This, together with much additional nce, suggests that elution is dependent upon action of the red-cell receptors by a thermolabile enzyme, and this view is now generally accepted.

e addition of a specific antiserum to a reaction re prevents hæmagglutination due to blockage of irus receptors by the antibodies. In the *normal* sera ny animal species there are substances which inhibit agglutination in a similar way by blocking virus tors; but these are relatively ineffective against g virus, whilst often inhibiting hæmagglutination eated virus to phenomenally high titres. Such con- ents of normal sera are termed serum inhibitors. lar inhibitors are present in other biological materials as egg white, and all of them probably owe their cy to a chemical and structural similarity to the ell receptors. Besides being able to unite, as red-cell tors do, with the virus receptors, they are likewise eptible to rapid destruction by living virus enzyme.

he hæmagglutination reaction is now very widely for many practical purposes. It provides a rapid hod of measuring the amount of virus in any preparation; or of titrating the antibody content of immune or the inhibitor content of normal sera. It is one of best methods of purifying and concentrating virus. e important, however, than such practical applica- s, influenza virus hæmagglutination gives us a model ome of the reactions between virus and host cell ch occur in the initial stages of the process of infection. as been shown that virus becomes similarly attached and then eluted from, the cells of tissues susceptible irus infection, like the mouse lung and the chorio- toic membrane of the chick embryo, and that ruction of the cell receptors renders such tissues non- eptible to infection (Hirst 1943, Fazekas 1948, Stone 8). It is therefore not unreasonable to suggest that lifications of the viruses which affect their hæmagglu- tion behaviour are likely to be the sort of modification h may affect functions involved in their infectivity virulence.

NTANEOUS MUTATION AFFECTING HÆMAGGLUTINATION BEHAVIOUR

lodification affecting hæmagglutination behaviour uently occurs when a virus is adapted to a new ronment. For example, Burnet showed that strains hly isolated from human cases usually agglutinate an or guineapig red blood-cells more readily than they fowl cells. Routine egg passage, however, results in eat increase of potency against fowl cells without any equivalent increase of potency against the cells of the other two species (Burnet 1943). Again Chu has recently reported that mouse adaptation of an egg strain is associated with a reduction of sensitivity of the virus to the inhibitors of normal mouse sera and that the change is reversible so that passage back again through eggs restores sensitivity (Chu 1951).

Some time ago we noticed that our standard egg-passage strain of PR8 virus had suddenly become much less susceptible to inhibition both by specific antibodies and by the normal serum inhibitors of various animal species (Smith et al. 1951a). In this case there was no question of a change of environment being responsible, for the virus had been maintained over a period of years by serial allantoic passage. Fortunately we were able to resuscitate the parent virus from freeze-dried material and it has been maintained by passage without, to date, any repetition of the spontaneous change of behaviour. Thus the two strains—the parent, which we labelled PR8/stock, and the mutant, referred to as PR8/X—could be studied side by side under strictly comparable conditions. It was found that they differed in their responses to heat treatment. The hæmagglutinating activity of the X mutant was much more heat-stable. With both viruses prolonged heating at 56°C resulted in progressive diminution of hæmagglutinin titre, but it took much longer to inactivate X completely than it did to inactivate stock. The most striking change was in the hæmagglutination inhibition of the heat-degraded viruses by normal serum inhibitors. It will be remembered that heat-treated viruses are usually much more sensitive to inhibitors than living viruses so that very much less inhibitor may be required to neutralise an equivalent agglutinating dose. Thus against a fixed dose of, say, four agglutinating doses of virus a serum may give against living virus an inhibitory titre of 1 in 50, but against a heated virus a titre of 1 in 2000. This phenomenon is known as the Francis phenomenon or Francis effect after its discoverer (Francis 1947). PR8/X consistently gave extremely poor Francis effects in comparison with the parent strain PR8/stock. The results of three comparative experiments are given in table I.

The natural assumption was that either a different virus had got into our eggs as a laboratory contaminant and replaced our standard PR8 strain or that a chance antigenic mutation had occurred. Both these possibilities were refuted by the most rigorous cross-immunity tests performed by more than one technique. So far as it was possible to determine, PR8/stock and PR8/X proved to be antigenically identical viruses.

MECHANISM OF THE FRANCIS PHENOMENON

This study of our laboratory mutant provided clear evidence that non-antigenic changes affecting virus hæmagglutination behaviour may not only be readily induced by altering the growth environment under experimental conditions but may also occur spontaneously within a stable environment. If such changes can occur during egg-to-egg transmission there is little doubt that they may also occur during man-to-man transmission in Nature, and the biological significance of hæm-

TABLE I—SPONTANEOUS MUTATION OF PR8 VIRUS AFFECTING INHIBITOR SENSITIVITY

Normal sera	Serum titres against 4 A.D. virus			
	PR8/stock		PR8/X	
	Living	Heated	Living	Heated
Guineapig ..	136	691	<20	40
Rabbit	80	1076	21	40
Human	297	877	55	58

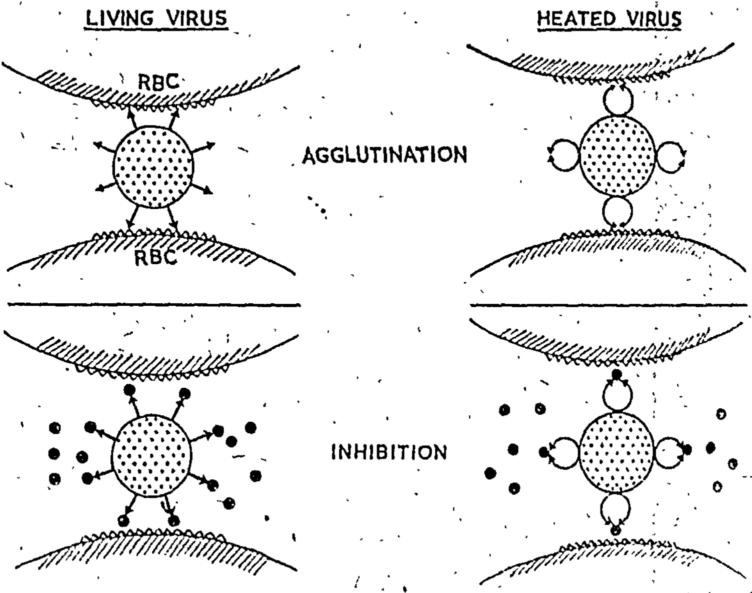


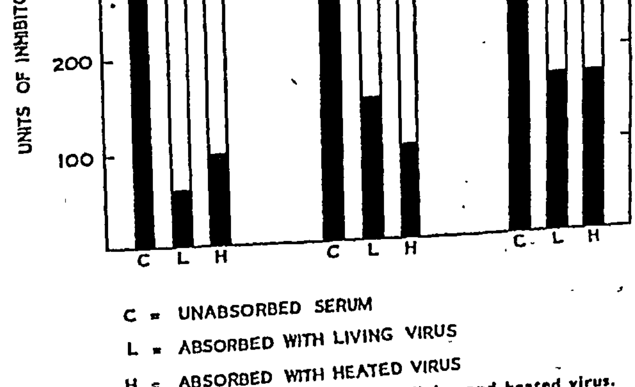
Fig. 2—Virus plasticity. Effect of distortion of surface configuration on inhibition of hæmagglutination.

agglutination reactions calls for an understanding of the factors underlying virus modifications of this type. We approached the problem by a detailed study of the mechanism of the Francis phenomenon. Why should 4 A.D.s (agglutinating doses) of heat-treated virus be inhibited by a mere fraction of the amount of serum required to inhibit 4 A.D.s of the same virus before heat treatment?

At the time we began the investigation the most widely accepted view was that the phenomenon was due to heat destruction of the heat-labile virus enzyme. Not only can this virus enzyme destroy red-cell receptors, resulting in elution of the virus after hæmagglutination has occurred, but it also destroys the inhibitors of animal sera and other biological fluids. Thus, according to this theory living virus, by virtue of its enzyme, rapidly destroys inhibitor molecules which block its receptors and so becomes free again to attach itself to red cells. Heated virus devoid of enzyme cannot do so and thus its receptors remain permanently blocked with inhibitor. Unfortunately for this attractive hypothesis the Francis effect occurs just as well at 0°C as at room-temperature though the enzymic activity of the virus is virtually abolished at the lower temperature. Subsequently we were able to deliver the final blow to the hypothesis by demonstrating that ether-extracted viruses give every bit as good Francis responses as heated viruses whilst retaining their full enzymic activity.

An alternative explanation put forward by Burnet and his associates was to the effect that red cells and inhibitor molecules compete for attachment to the virus receptors and that heat treatment of a virus increases its affinity for inhibitor relative to its affinity for the red cell (Anderson et al. 1948).

To put this hypothesis to crucial test some means had to be devised of measuring the actual amounts of inhibitor taken up by equivalent doses of living and heated virus. It was found that free inhibitor molecules would pass freely through filter membranes which would hold back virus particles. Thus after absorption of a serum with either living or heated virus any residual unbound inhibitor could be recovered by filtration and titrated. A simple subtraction sum then gave the precise amount which had been absorbed by the virus.



by living and heated virus.

The results of three experiments of this type, in all of which equivalent hæmagglutinating doses of living and heated virus absorbed the same amounts of inhibitor within the limits of experimental error, are illustrated by fig. 1. One experiment was done with fowl cells present in the reaction mixtures and one experiment with human red cells present. This was to check the hypothesis that the dynamic equilibrium between cells virus and inhibitor determined the amount of inhibito absorption. Quite clearly the presence or absence of re cells made no difference. We then proceeded to investigate the time factor in this heat-induced virus change Using both PR8 stock virus and its X mutant which mentioned earlier we carried out a large number o experiments in which the viruses were heated at 56° for several hours, samples being withdrawn at interval for estimations of both hæmagglutination titre and o susceptibility to inhibition by a normal serum.

Continued heat treatment results in a progressiv decrease of hæmagglutinating potency until all agglu tinating activity is lost. But the less active the viru becomes the more susceptible is it to inhibition by serum for against a standard hæmagglutinating dose of 4 A.D of virus serum titres go on increasing the longer th virus is heated. Finally of course there comes a poin when complete destruction of virus receptors prevent further serum titrations.

On the basis of these and numerous other experiment we put forward what is conveniently termed the Hypothesis of Steric Hindrance (Smith and Westwood 1950) This assumes that continued heat treatment results i progressive distortion of the surface configuration of th virus up to a point when the receptors are finally destroye so that hæmagglutinating activity is completely los This distortion permits molecules of inhibitor, blockin a receptor to which they are attached, to block als neighbouring receptors by preventing that close appos tion to the red-cell surface which is required for actu linkage to occur. Thus one molecule of inhibitor again heated virus may do the work which requires severa molecules in the case of living virus. Distortions pro duced by other agents like ether will have the sam effect as regards susceptibility to inhibitor but may have no effect upon other virus components like the receptor-destroying enzyme. The theory is graphically represented by fig. 2.

I believe this hypothesis to be at least a close approximation to the truth, because it fits all the known facts providing a satisfactory explanation for the following: (1) the Francis phenomenon; (2) the progressive fall of virus hæmagglutination titres on heating; (3) the progressive increase of Francis effect on continued heating; (4) the occurrence of the Francis phenomenon at low temperature, and (5) the production of indicator virus by ether extraction without loss of enzymic activity.

If we accept this explanation a number of very important implications may be logically deduced.

1. Different hæmagglutination behaviour of different influenza viruses, or of the same virus adapted to different hosts, may depend upon differences of surface configuration rather than upon differences of chemical or antigenic constitution.

2. Changes of surface configuration which affect virus red-cell reactions are likely to affect also the reactions between virus and susceptible host cell in the early stages of the infection process. Thus they may determine the virulence, communicability and host range of the virus.

3. Architectural modifications may occur in a stable environment by the process of chance mutation but this is probably an extremely rare occurrence.

4. The fact that a change of growth environment invariably results in some change of biological activity suggests that virus architecture depends to some extent upon the species of host or type of host tissue in which the virus is propagated.

I believe that this last implication poses one of the most fundamental problems in virus research. Can any light be shed on the mechanisms by which architectural modifications are brought about?

HOST PROTEIN AS AN INTEGRAL PART OF THE VIRUS

As is often the case in biological research, a lead came from experiments which were designed to quite other purpose. It had always seemed to me improbable that two viruses like influenza type A and influenza type B should cause indistinguishable human infections, and also possess many major biological attributes in common, without there being some phylogenetic relationship between them. We hoped to demonstrate such relationship by unmasking deep common antigens on the lines so successfully exploited by Bruce White in the case of the salmonella group of bacteria. The progressive degradation of surface components which occurs on heat treatment suggested the possibility of common, heat-stable, somatic antigens being demonstrable in cross tests with heated viruses and antisera prepared against them. Heating influenza viruses at 60°C for varying periods according to the particular strain completely destroys their type-specific surface antigens. Such heated viruses, however, will still give complement-fixation with their homologous antisera. We found that they would also give fixation with sera of the heterologous type; that is to say, there were good cross reactions between types A and B.

The most likely explanation was, of course, that the cross reactions were due to contaminating antigenic material derived from the eggs in which the viruses had been grown. By using control antigens made from extracts of chorio-allantoic membranes from uninfected eggs it was soon found that most of the cross reaction was in fact due to egg material and anti-egg immune bodies in the virus antisera. At first sight this seemed to settle the matter, but there remained the puzzling fact that for clear demonstration of cross reaction heat-degradation of the viruses was required. This did not seem to fit in with the idea that the common antigen was merely egg material free in the allantoic fluid or even adsorbed onto the virus surface. It suggested rather that it was deeper in the virus structure, requiring surface degradation for its exposure. It raised the dominant question: "Is the egg antigen, which is responsible for cross reactions between A and B viruses, a wholly independent contaminant or is it an integral component of the virus structure?"

The idea that viruses may *contain a host protein* component was not a new original idea of our own. Knight some years ago found that no matter how thoroughly he attempted to purify an influenza virus a host antigen remained demonstrable by precipitation tests. Virus grown in eggs gave reactions with anti-egg sera; virus grown in mice reacted with anti-mouse sera. Yet by every physical test, including electrophoretic mobility, his preparations appeared to consist solely of homogeneous infective virus particles. He suggested that the host material must be an integral part of the virus elementary body and calculated that it must represent up to 20% or more of the virus mass (Knight 1946). In view of the revolutionary nature of this conception and its tremendous implications I must confess to some surprise that it has not received much more attention by virus workers. The reason probably is that virus purification by physical means, however thorough, can never wholly refute the criticism that contaminant material may remain evenly and firmly adsorbed onto the surfaces of the virus particles. What we are now attempting is to demonstrate that A and B viruses obtained in as pure state as possible, by a combination of centrifugation and red-cell agglutination and elution methods, will show no cross reactions until they are disrupted by means such as heat which destroys their surface. This appears to have been successful in a few of our experiments, one of which is summarised in table II. Such results make it difficult to refute the conclusion that the host protein responsible for the cross relationship is incorporated as such into the virus structure. Much further evidence is, of course, required in order to constitute definite proof; but perhaps I may be allowed to summarise the evidence so far obtained:

TABLE II—CROSS C.F. REACTIONS BETWEEN INFLUENZA VIRUSES TYPES A AND B

Antisera	Antigens			
	Living viruses		Heated viruses	
	PRS A	Lee B	PRS A	Lee B
PRS A	++++	0	++	++
Lee B	0	++++	++	+++

+ signs indicate the degrees of complement fixation.

1. In some experiments purified living A and B viruses show either no cross complement-fixation or a mere trace. When they are heated, however, there is very strong cross reaction.
2. The cross reactions are chiefly though not wholly due to an antigen present in normal chorio-allantoic membrane for antisera absorbed out with extracts of this membrane lose most of their reactivity.
3. A totally unrelated virus, that of Newcastle disease of fowls, when grown in eggs, reacts with an influenza virus antiserum provided that the virus is first heated.
4. Successive purifications of an influenza virus by repeated red-cell agglutination and elution are found to contain progressively less allantoic fluid material whilst retaining cross reactivity to the full.

THE REPLICATION OF INFLUENZA VIRUSES

The idea of host protein as such, and with retention of its immunological specificity, being incorporated into the virus structure is probably difficult to accept because of a deeply ingrained belief that binary fission, as displayed by the majority of the bacteria, must be the normal mode of reproduction for asexual organisms of this order of size. Little is known about the mechanism of virus multiplication, but in the case of the influenza viruses there is a growing body of evidence suggesting that they must have evolved a mechanism quite different from simple binary fission.

It has been shown by Hoyle (1948) in this country, Magnus (1951) in Denmark and the Henles (1949) in U.S.A. that virus inoculated into the allantoic cavity of the chick embryo first disappears, so that it cannot be recovered from either the allantoic fluid or from the membrane lining the cavity. Preceding the reappearance of infective virus the allantoic fluid acquires first the complement-fixing activity which we associate with soluble virus antigens, then the complement-fixing activity associated with surface virus antigens, and then hæmagglutinating activity. Finally a great increase of infectivity occurs. Magnus indeed claims that by varying the technique of passage inoculation he can obtain at will allantoic fluids with either a very high content of infective virus or with a very low infectivity titre combined with a high hæmagglutination titre. He postulates that either fully developed infective virus or incomplete immature virus devoid of infectivity can agglutinate red blood-cells, and he calculates that some of his allantoic fluids contained only 1 fully developed infective elementary body to about 10,000 incomplete hæmagglutinating particles.

These facts certainly do not accord with reproduction by simple binary fission, and they have led to the hypothesis that infective virus which invades susceptible host cells breaks up into a number of non-infective sub-units which replicate themselves at the expense of the cell economy. Finally the sub-units aggregate into the characteristic pattern which represents fully formed infective virus elementary bodies. Burnet and Lind (1951) have adopted a similar hypothesis of virus reproduction in order to explain the origin of recombinant virus strains derived from two parent strains possessing distinctive marker characters when these are inoculated together in embryonated eggs. The recombinant viruses are found to have heritable characteristics derived from each of the parents and are considered by Burnet to represent organised elementary bodies built up from a mixture of the sub-units or building-stones of the progenitor viruses.

Whilst I am certainly not prepared to accept this hypothesis of influenza virus replication as proven, I regard the apparently unbreakable association of host protein with virus activity as further evidence in its support. During the stage of aggregation of virus sub-units into a pattern characteristic of the particular strain there would be every likelihood of some of the products of host-cell necrosis being caught up in the interstices of the virus structure.

HOST PROTEIN AS A DETERMINANT OF VIRUS ARCHITECTURE

So far I have been careful to draw a sharp line of demarcation between experimental facts, which whatever their meaning remain facts, and the interpretations of them which still leave room for doubt. At this point I would like to present a hypothesis which is purely speculative in order to attempt some sort of synthesis of the various phenomena we have been considering. I think this is justifiable because, when attempting to open up a new line of investigation, the design of fruitful experiments largely depends upon free speculation; and as long as hypothesis is always modified to fit new facts, instead of facts being twisted to suit hypothesis, no harm can result.

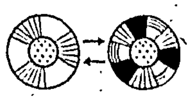
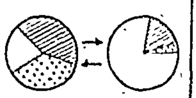
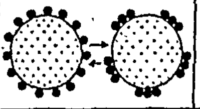
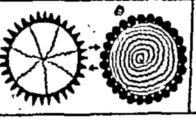
TYPE	COMPONENT INVOLVED	DIAGRAMMATIC REPRESENTATION	EXAMPLE
1	ANTIGENS GAIN OR LOSS		A AND A-PRIME
2	ANTIGENS CHANGE OF PROPORTIONS		A SUBSTRAINS
3	SURFACE CONFIGURATION		PR8 STOCK AND X MUTANT
4	HOST PROTEIN		PR8 VIRUS EGG AND MOUSE ADAPTED STRAINS

Fig. 3—Types of structural plasticity of influenza viruses.

The four major types of structural plasticity of the influenza viruses are illustrated in fig. 3. Why do these modifications occur and how are they brought about? There is abundant evidence that the mechanism of chance mutation due to genetic alteration followed by natural selection of the mutant is at work with the viruses as with all other forms of life. It may be that most of the antigenic variations depend upon such genetic mutation. We have seen, however, that relatively simple changes in surface configuration, such as may be induced by heat or other treatment, affect biological activity and that this type of change, though also occurring spontaneously from time to time, appears to result regularly from a change of growth environment and especially from a change of host species. It has always seemed to me that the frequency of virus modification and the regularity of its pattern on adaptation to a new host require more than selection of rare chance mutants as a satisfactory explanation.

I propose to accept provisionally the two hypotheses which I freely admitted have not yet been definitely proved—first that host protein is incorporated as an integral part of the virus unit, secondly that virus multiplication is based on the independent replication of sub-units followed by their aggregation into the characteristic pattern of the fully formed, infective elementary body. If this is so, it becomes inconceivable that the host protein should be without effect upon the general configuration of the virus. Even if the host moiety is present merely as a contaminant, included as it were by accident in the virus structure, the protein molecules of different animal species characterised by different molecular size, different chemical constitution and different molecular form would be expected to affect the pattern in which virus sub-units coalesced. May it not be that, far from being an accidental contaminant, host protein is essential for this fusion of virus components which comprise numerous antigens, surface receptors, enzyme groups, and so on? The host protein would thus serve as a sort of scaffolding or skeleton framework on which the organised living whole was constructed and in this way be a determinant of virus architecture. Furthermore, this would help to explain the progressive adaptation to a new species. The host component may be necessary to give the impress on the virus pattern required for the full utilisation of the new nutrient materials available. Until the new host-parasite relationship has become fully stabilised there may be a lack of synchronisation in sub-unit replication resulting in architectural flaws which in turn result in the production of much immature relatively inactive virus.

All this may seem a far cry from the urgent practical problem of the control of pandemic and epidemic influenza. Such control may possibly come from some chance discovery or by the application of purely empirical methods but I think it is more likely to require much fuller knowledge than we now possess about the nature of the causative viruses and the mechanisms underlying their variable biological activities. Moreover, any additions to knowledge of this kind cannot fail to have implications extending far beyond the limited field of influenza research.

Eventually man will achieve complete mastery over the micro-organisms which constantly threaten him. It is our hope that by pursuing the investigations which I have outlined we may be privileged to make some small contribution to this desired end.

My thanks are due to my collaborators Dr. G. Belyavin and Dr. J. C. N. Westwood for permission to discuss our unpublished work.

REFERENCES

Anderson, S. G., Burnet, F. M., Fazekas de St. Groth, S., McCrea, J. F., Stone, J. D. (1948) *Aust. J. exp. Biol. med. Sci.* 26, 403.
Burnet, F. M. (1943) *Med. J. Aust.* i, 385.
— Lind, P. E. (1951) *J. gen. Microbiol.* 5, 67.
Chu, C. M. (1951) *Ibid*, p. 739.
Fazekas de St. Groth, S. (1948) *Aust. J. exp. Biol. Med. Sci.* 26, 29.
Francis, T. (1940) *Science*, 92, 405.
— (1947) *J. exp. Med.* 85, 1.
— Salk, J. E., Quilligan, J. J. (1947) *Amer. J. publ. Hlth*, 37, 1013.
Henle, W., Henle, G. (1949) *J. exp. Med.* 90, 23.
Hirst, G. K. (1941) *Science*, 94, 22.
— (1943) *J. exp. Med.* 78, 99.
— (1947) *Ibid*, 86, 357.
Hoyle, F. (1948) *Brit. J. exp. Path.* 29, 390.
Knight, C. A. (1946) *J. exp. Med.* 83, 281.
Magill, T. P., Francis, T. (1936) *Proc. Soc. exp. Biol. Med.* 35, 463.
Magnus, P. von. (1951) *Acta Path. Microbiol. scand.* 28, 278.
McClelland, L., Hare, R. (1941) *Canad. publ. Hlth J.* 32, 530.
Rasmussen, A. F., Stokes, J. C., Smadel, J. E. (1947) *Amer. J. Hyg.* 47, 142, 1942.
Salk, J. E., Menke, W. J., Francis, T. (1945) *Ibid*, 42, 57.
Smith, W., Andrewes, C. H., Laidlaw, P. P. (1933) *Lancet*, ii, 66.
— — (1938) *Brit. J. exp. Path.* 19, 293.
— Westwood, J. C. N. (1950) *Ibid*, 31, 725.
— Westwood, M. A., Westwood, J. C. N., Belyavin, G. (1951a) *Ibid*, 32, 422.
— Westwood, J. C. N., Belyavin, G. (1951b) *Lancet*, ii, 1189.
Stone, J. D. (1948) *Aust. J. exp. Biol. med. Sci.* 26, 49.
Sugg, J. Y. (1949) *J. Bact., Baltimore*, 58, 399.
Taylor, R. M. (1949) *J. Amer. Publ. Hlth Ass.* 39, 171.

SUBDURAL EFFUSIONS IN PURULENT MENINGITIS

H. Everley Jones
O.B.E., M.B. Lond., M.R.C.P.
PHYSICIAN TO CHILDREN'S DEPARTMENT, THE ROYAL HOSPITAL, WOLVERHAMPTON

Until recently almost all cases of pyogenic meningitis, except those due to the meningococcus, were fatal. With sulphonamides and antibiotics survival is now expected, even in infants, and the study of complications and sequelæ has therefore become important.

A condition lately described in association with purulent meningitis is the subdural collections of fluid (McKay et al. 1950, Smith et al. 1951, and Arnold 1951). The first to report subdural suppuration arising from purulent leptomeningitis seem to have been Spitz et al. (1945) who recorded two cases with subdural collections of fluid found at necropsy. Three other cases mentioned in their series had infection in the middle ear or nasal sinuses which might have been responsible for the effusions, as described by Penfield (1923). All these reports are American, and I have found no British account of subdural effusion as a complication of purulent meningitis.

During the past 9 months, I have treated twelve cases of purulent meningitis in infants between the ages of 3 weeks and 11 months; and in six I have found subdural collections of fluid.

CASE-REPORTS

Case 1.—A girl, aged 5 months, was admitted to hospital after 14 days' irritability and 2 days' lifelessness, vomiting, and diarrhœa. 'Sulphamezathine' had been given for 1 day.

Examination.—Weight 15 lb. 4 oz.; irritable; fontanelle bulging; neck rigid; pupils pin-point. Cerebrospinal fluid: pressure increased; cells 4000 per c.mm.; protein 200 mg. per 100 ml.; sugar 30 mg.; sterile on culture.

Treatment and Progress.—Penicillin, 100,000 units intramuscularly every 4 hours and 10,000 units intrathecally daily, was given for 6 days, with sulphamezathine (0·25 g.) every 4 hours. The child's condition did not improve and the temperature remained raised. On the 5th day in hospital streptomycin 150 mg. was given intramuscularly every 12 hours and on the 7th day chloromycetin 125 mg. 6-hourly by mouth was tried, without much improvement; the fontanelle was still tense.

Subdural Taps.—On the 14th day 17 ml. of cloudy yellow fluid, under increased pressure, was obtained by subdural tap on the left side, and 6 hours later 20 ml. of similar fluid from the right side. It contained a few lymphocytes, protein 1000 mg. per 100 ml., sugar 50 mg., and it was sterile on culture. Improvement was immediate: the fontanelle became flat and the temperature settled. The appearance of anxious misery disappeared and medical treatment was stopped. A further fourteen subdural needlings were done, at first daily, then on alternate days. On the right side only four were productive, but on the left each tap produced from 23 ml. to 50 ml. of xanthochromic fluid, with a maximum protein content reaching 2100 mg. per 100 ml. An air encephalogram on the 26th day showed no hydrocephalus, but on a plain film an air-containing space was seen over the left parietal cortex. Exploration on the 32nd day revealed a subdural collection of fluid bulging through the left coronal suture. The base of the sac formed by a thin grey membrane was left undisturbed during removal of fluid containing 2700 mg. per 100 ml. of protein. The brain re-expanded, no further fluid was obtained, and the baby made an uneventful recovery.

Follow-up at 11 months revealed a child normal for her age.

Case 2.—A boy, aged 11 months, had been ill for 3 days with irritability, head-shaking, and vomiting.

Examination.—Weight 19 lb.; very irritable; fontanelle bulging; neck rigid; conjunctivitis right eye. Cerebrospinal fluid: pressure normal; turbid; cells 5300 per c.mm.; protein 156 mg. per 100 ml.; sugar reduced; sterile on culture.

Treatment and Progress.—Intramuscular penicillin 25,000 units, and 'Sulphatriad' 0·5 g., were given every 6 hours for 14 days. On the 3rd day in hospital the patient's condition was unchanged.

Subdural taps produced no fluid from the left side, but from the right side 12 ml. of sterile turbid fluid containing 650 cells per c.mm., protein 156 mg. per 100 ml. Next day the temperature fell and the child's condition improved. On the 6th day 23 ml. was obtained from the right side (cells 200 per c.mm., protein 88 mg.). Cerebrospinal fluid from lumbar puncture at this time contained 44 cells per c.mm. and protein 60 mg. Three further subdural taps on the 9th, 13th, and 20th days yielded progressively decreasing amounts. On the 26th day taps on both sides were unproductive. Tenseness of the fontanelle persisted for 12 days.

$2^{1}/_{2}$ months after discharge the child appeared mentally and physically normal.

Case 3.—A girl, aged 6 months, was admitted after 24 hours' fever and irritability. She had had a generalised convulsion shortly before admission and had had a cough for 3 weeks.

Examination.—Weight 18 lb. 4 oz.; bronchopneumonia; no meningeal signs. Next day there was slight neck rigidity and fullness of fontanelle. Cerebrospinal fluid: cloudy; cells 3100 per c.mm.; protein 250 mg. per 100 ml.; sugar 42 mg.; *Hæmophilus influenzæ* isolated on culture.

Treatment and Progress.—She was given sulphamezathine 0·5 g. every 4 hours for 16 days and chloramphenicol 150 mg. every 4 hours (tapering to 25 mg. every 4 hours) over 5 days. The cerebrospinal fluid was rapidly sterilised but the temperature remained raised and the child was still irritable.

Subdural taps on the 4th day produced 9 ml. of opalescent straw-coloured fluid from the left side but none from the right. This fluid was sterile and contained 1000 cells per c.mm., protein 2400 mg. per 100 ml., sugar 43 mg. The child improved somewhat but the temperature remained raised. On the 5th day 20 ml. of fluid was removed from the left side. Two further attempts were unsuccessful, yet the child continued to be unwell, with a raised temperature and a full fontanelle for 10 days. A ventricular puncture was then done, after which she made a good recovery and was discharged on the 25th day.

2 months later she appeared to be a normal child.

Case 4.—A boy, aged 5 months, was admitted with a 5-day history of malaise and heavy breathing, thought to be pneumonia.

Examination.—Weight 13 lb. 2 oz.; drowsy; irritable when disturbed; slight neck rigidity; fontanelle tense. Cerebrospinal fluid: pressure greatly increased; turbid; cells 4200 per c.mm.; protein 125 mg. per 100 ml.; sugar 19 mg.; *meningococci* isolated.

Treatment and Progress.—He received intramuscular penicillin 50,000 units every 6 hours and sulphamezathine 0·5 g. every 4 hours for 36 hours, followed by 0·25 g. every 4 hours for 12 days. Response to treatment was slow: the temperature did not settle until the 9th day.

Subdural taps on the 11th day produced 8 ml. of slightly yellow opalescent fluid from the right side, but none from the left side. This fluid contained 85 cells per c.mm., protein 200 mg. per 100 ml., and glucose 33 mg.; sterile. Cerebrospinal fluid obtained by lumbar puncture about the same time showed 3 cells per c.mm. and protein 150 mg. per 100 ml. A tap on the 14th day produced 4 drops of clear colourless fluid. Recovery was uneventful.

3 months later the child was physically and mentally normal.

Case 5.—A boy, aged 5 weeks, had been fretful and refusing food for 3 days before admission to hospital. He had had frequent convulsions for 2 days.

Examination.—Weight 9½ lb.; semicomatose; Cheyne-Stokes breathing; fontanelle bulging; neck stiffness present. Cerebrospinal fluid: only a few purulent drops withdrawn; meningococci isolated.

Treatment and Progress.—Sulphatriad 0·5 g. was given every 4 hours for 20 days and penicillin intramuscularly, at first 500,000 units every 4 hours and later 500,000 units twice daily. Very slow progress was made and on the 10th day of treatment the cerebrospinal fluid contained 1500 cells per c.mm. and protein 200 mg. per 100 ml.

Subdural taps on the 11th day yielded 3 ml. of yellow fluid from both sides. The temperature fell and the fontanelle became less tense. On the 18th day 12 ml. of xanthochromic fluid was recovered from the left side. Further productive taps were made on the left side on the 20th day (15 ml.), the 22nd day (15 ml.), the 24th day (7 ml.), and the 26th day (4 ml.). Two later attempts were unsuccessful. These specimens, which were all sterile, contained about 3000 mg. per 100 ml. (maximum 3200 mg.) of protein and a few cells. 3 days after the last productive tap the cerebrospinal fluid from lumbar puncture contained 20 cells per c.mm. and protein 120 mg. per 100 ml. Before discharge from hospital an air encephalogram showed a normal ventricular system.

Follow-up at 3 months of age showed an apparently normal infant.

Case 6.—A boy, aged 8 months, was admitted after 4 days' malaise, restlessness, and vomiting.

Examination.—Weight 19 lb. 13 oz.; listless; marked neck rigidity; fontanelle bulging. Cerebrospinal fluid: pressure increased; cells numerous; protein 60 mg. per 100 ml.; meningococci present.

Treatment and Progress.—He was given sulphamezathine 1 g. every 6 hours for a week, followed by chloramphenicol 250 mg. every 4 hours (for diarrhœa). Two intrathecal injections of 10,000 units of penicillin were followed by no improvement; on the 4th day of treatment restlessness was pronounced and the fontanelle was tense. Cerebrospinal fluid from lumbar puncture contained 85 mg. per 100 ml. of protein and 67 mg. of sugar.

Subdural taps on the 4th day yielded no fluid on the left side, but 9 ml. of cloudy yellow fluid was obtained from the right: this was sterile but under greatly increased pressure; the protein content was 1000 mg. per 100 ml. and sugar 166 mg. The child's restlessness soon decreased but the temperature rose again after a temporary fall. This fever may have been related to the onset of an intense diarrhœa 36 hours later. On the 5th day 10 ml. of subdural fluid was removed from the right side and 13 drops from the left side, under normal pressure and almost clear. Two later taps were unproductive. Convalescence was prolonged by diarrhœa and upper respiratory infection, which probably accounts in part for slight backwardness a month later.

In six other children (aged 5 weeks to 5 months) with purulent meningitis, bilateral subdural taps yielded no fluid. In one case the causal organism was not identified; in three it was *Bacterium coli*, in one it was a pneumococcus, and in one a meningococcus.

COMMENT

The amount of fluid present in the normal subdural space is not known. Samson Wright (1948) says: "a very small amount resembling lymph" and Ingraham and Matson (1949) allow up to 1 ml. of clear colourless fluid with a low protein content. In practice it is difficult to withdraw any fluid from this space in normal infants.

In previously recorded cases of subdural effusion the organism causing the meningitis has been *H. influenzæ* in twenty cases, a pneumococcus in twelve, a paracolon bacillus in one, and *Pseudomonas æruginosa* in one.

In one case both *H. influenzæ* and a pneumococcus were found. It will be noted that the meningococcus was not recovered in any of these previously recorded cases, whereas in the present series it was found in three. Of my two cases in which no organism was recovered, sulphonamide was administered to 1 before admission and may have been administered to the other. So either may have had a meningococcal infection.

Severely ill children appear to be most likely to suffer this complication: only three of the largest series recorded—the twenty cases of Smith et al. (1951)—were regarded as mildly ill. The type of treatment seems to have no bearing on the development of an effusion; nor does the time of illness when therapy is started appear to be a factor, for, in my cases, the patients developing this complication started treatment slightly earlier than the others.

In most patients subdural fluid has been found during the first fortnight of the disease, but it may be found up to the 62nd day, as in a case reported by Smith et al. (1951). It is difficult to know how soon fluid may accumulate; in the present series the earliest positive tap was made on the 4th day of the disease.

The amount of fluid ranges from a few drops to over 50 ml. at a time and may be found on one or both sides. The fluid is nearly always yellow (but later may become clear) and the protein content in the early stages is considerably higher than in cerebrospinal fluid withdrawn at the same time. Arnold (1951) distinguishes the clear serous sterile fluid, with a low content of cells, from the cloudy fluid, with a high cell content, from which bacteria may be cultured. Both are yellow and both have a protein content as high as 3 g. per 100 ml. or more. It is doubtful whether such a sharp distinction can be made, and organisms have rarely been isolated from the fluid.

The clinical indication for subdural taps is unexplained failure to make the expected response to adequate treatment by the 3rd day. The small experience of the present series suggests that a continued or rising pyrexia associated with restless anxiety often indicates pressure from subdural fluid. In most cases the fontanelle is tense or bulging. Convulsions have ceased after the removal of subdural fluid: perhaps the regular administration of phenobarbitone in the present cases has also helped to prevent them. No changes have been noted in the optic fundi and there has been no increase in the circumference of the head. There are also cases (e.g., no. 4) in which subdural fluid produces little clinical evidence of its presence. In two of the four cases described by Arnold (1951) an area of erythema and œdema was found near the anterior fontanelle; but this sign was not found in any of the present series.

Pathology

As Smith et al. (1951) point out, the cause of subdural effusions in meningitis is unknown. These effusions, however, are not unlike the subdural hæmatoma of infants, in which a head injury, often slight, at birth or later, causes bleeding into the subdural space. The hæmatoma becomes encapsulated, and, as the red cells break down, the rising osmotic pressure within the capsule causes fluid to pass in through the capsule (Ingraham and Matson 1949). It is possible that in meningitis the arachnoid is damaged and allows the passage of a fluid rich in protein which increases in volume by osmosis. The observed presence of a membrane in case 1 and the invariably high protein content of the fluid support this view. In both conditions the effusion assumes a pancake shape over the parietal lobe and extends forwards towards the frontal lobe.

To make sure that the effusion was confined to the subdural space, indigo carmine was injected into the effusion on the left side in case 1. Cerebrospinal fluid withdrawn later by lumbar puncture showed no trace of dye, while at the same time a subdural tap on the left side produced a deeply stained fluid. Thus there was no communication between the subdural and subarachnoid spaces.

That these effusions cannot be attributed to therapeutic intrathecal injections is shown by case 3 in which the child was treated with sulphamezathine and chloramphenicol given only by mouth.

Treatment

Subdural taps were made at the lateral angle of the anterior fontanelle or through the coronal suture half an inch from the lateral angle of the fontanelle. To minimise the risk of cerebral œdema, the fluid was allowed to drip out through the needle without aspiration. For the same reason, if a large quantity of fluid was obtained from one side, the other side was not tapped at the same time. The intervals between tappings varied, but when a large amount of fluid was found the tap was repeated at about 2-day intervals. Usually the subdural space can be emptied after two or three taps but if fluid persists after repeated taps over a period of weeks, as in case 1, operation must be considered. If the brain does not re-expand after the fluid has been removed dissection of the underlying membrane may be required, as in the case of subdural hæmatoma (Ingraham and Matson 1949).

In view of the apparently high incidence of this complication in cases of purulent meningitis in infants, diagnostic needling of the subdural space should be done in every patient who has not responded satisfactorily to adequate treatment by the 4th day. (Subdural effusion has not been reported in tuberculous meningitis; negative taps were made in three cases of my own.)

Although, so far, subdural effusions have been found only in infants, the condition may occur in older subjects in whom the fontanelles are closed. If such patients present a similar clinical picture it would seem reasonable to make exploratory burr-holes.

SUMMARY

Of twelve cases of purulent meningitis in infants between the ages of 3 weeks and 11 months, six had subdural effusions. Continued fever associated with restless anxiety and tense fontanelles after 3–4 days of adequate therapy is an indication for needling the subdural space. Repeated taps may be necessary to remove all the fluid. Recovery is usually rapid and uneventful.

I should like to express my thanks to Mr. C. Vincent Patrick, senior surgeon to the Royal Hospital, Wolverhampton, for the operation in case 1, and to Dr. J. Garvie, pædiatrician to the Walsall Group of Hospitals, with whom case 5 was treated.

References at foot of next column

DAILY URINARY 17-KETOSTEROID OUTPUT OF AFRICAN NEGROES

N. A. BARNICOT
B.Sc. Lond, Ph.D.

DAVIDA WOLFFSON
M.A. Chicago

From the Department of Anthropology, University College, London

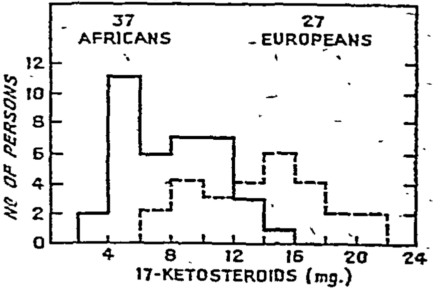
IN the course of examining the daily urinary 17-ketosteroid output of African Negroes as a preliminary to work on climatic physiology, we were struck by the remarkably low values encountered in some of them. Unable to find any published report of the 17-ketosteroid output of Negroes, we undertook a more extensive and systematic comparison of African and European males.

MATERIAL

The results reported here are based on a sample of 37 West Africans and 27 Europeans. The mean age of the Africans was 30·25 years, $\sigma = 4{\cdot}74$; and of the Europeans 27·29 years, $\sigma = 4{\cdot}38$. The Negro sample consisted of 24 students who had been resident in London from one to six years; 6 medical students at the Adeoyo Hospital, Ibadan, Nigeria; and 7 employees of the Hot Climate Physiological Research Unit, Oshodi, Lagos, Nigeria. The European sample comprised 21 students or members of the academic or technical staff of University College, London; 2 members of the staff of the Hot Climate Physiological Research Unit, Oshodi, who had been resident only a few months in Nigeria; and 4 research-workers, examined both in London and Nigeria. The Negro and European samples were collected concurrently over about eighteen months.

METHOD

Since it is generally recognised that the collection of 24-hour specimens of urine is liable to be inaccurate, we chose, so far as possible, only those persons whom we judged to be reliable, and tried to impress on them the need for obtaining a complete sample. As a check on the reliability of collection we also determined the creatinine content of the specimens. 6 of the Hot Climate Physiological Research Unit employees remained under supervision in the laboratory over the period of collection. The urine was collected and stored under toluene in the refrigerator if immediate extraction was impossible. The 17-ketosteroids were assayed by Callow's modification of the Zimmermann reaction (Callow et al. 1938), as described by Warren (1950).



Daily urinary excretion of 17-ketosteroids.

RESULTS

The results are presented in the accompanying figure. The mean 24-hour output of the Africans was 7·97 ±

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Arnold, G. G. (1951) *J. Pædiat.* 39, 191.
Ingraham, F. D., Matson, D. D. (1949) Advances in Pediatrics. London and New York; vol. 4, p. 231.
McKay, R. J., Morisette, R. A., Ingraham, F. D., Matson, D. D. (1950) *New Engl. J. Med.* 242, 20.
Penfield, W. G. (1923) *Amer. J. Dis. Child.* 26, 291.
Smith, M. H. D., Dormont, R. F., Prather, G. W. (1951) *Pædiatrics*, 7, 34.
Spitz, E., Pollak, A., Angrist, A. (1945) *Arch. Neurol. Psychiat.* 53, 144.
Wright, S. (1948) Applied Physiology. London.

0·48 mg., σ = 2·89 mg.; and of the Europeans 13·71 ± 0·72 mg., σ = 3·76 mg. The European mean lies close to the values given by other workers using essentially the same method (Mason and Engstrom 1950). A "t" test on the means for Africans and Europeans gives t = 6·91, which for 62 degrees of freedom is significant at more than the 0·001 level. It will be noticed that 13 (35%) of our Africans gave a daily output of less than 6 mg., a range which might suggest abnormality in a European male. In 4 cases we checked these unusually low outputs by examining a second specimen from the same person, and we found closely similar values.

It is known (Robinson 1948, Hamburger 1948, Konigsberg et al. 1949) that the output of 17-ketosteroids changes with age. The precise shape of the curve at the age of 20–40 cannot be established on the existing data, but it seems unlikely that the difference of mean age between our samples could be responsible for a difference of more than 1 or 2 mg. of 17-ketosteroids at the most. It is also improbable that inaccurate collection of the urine could explain the result, since the mean creatinine outputs for the two groups were not significantly different (Africans 1·80 ± 0·7 g., σ = 0·38 g.; and Europeans 1·90 ± 0·07 g., σ = 0·37 g.) and lie within the range commonly regarded as normal for European males. Nor is it likely that climatic differences played a significant part, since there was no demonstrable difference between the mean output of 17-ketosteroids in the 24 Africans resident in London (7·83 ± 0·57 mg.) and the 13 resident in Nigeria (8·17 ± 0·87 mg.).

EFFECT OF TESTOSTERONE

A low daily excretion of 17-ketosteroids has been reported in various diseased states apart from those primarily involving the pituitary, adrenal cortex, and testis—such as chronic and acute liver diseases, gout, various infections, malnutrition, and debilitating diseases in general (Forbes et al. 1947, Fraser et al. 1941). Our subjects were free from overt illness, so far as could be determined without clinical examination, and were all leading normal active lives. Nevertheless, in view of the prevalence of nutritional deficiencies and parasitic diseases in Africa, the possibility that they might have sustained some damage from these agencies in childhood should be considered. We therefore thought it worth while to examine the effect of testosterone on the 17-ketosteroid excretion of Africans. Previous work on this subject concerns mainly the response of hospital patients with various liver dysfunctions and other severe conditions (Engstrom et al. 1951, West et al. 1951, Rupp et al. 1951, Bjorneboe et al. 1950), and it has been shown that in them the increased output of urinary 17-ketosteroids after a given dose of testosterone is less than in normal people owing, it is supposed, to a decreased ability of the liver to convert testosterone to these particular end-products.

Material.—Seven Africans on the staff of the Hot Climate Physiological Unit, Oshodi, were tested in Nigeria with two Europeans who had been in Nigeria only a few months, and five European students were later tested in London. Six of the Africans, who had been recruited to the unit from the Lagos labour force, remained under supervision in the laboratory during the five days of the experiment, and estimations of creatinine on the 24-hour samples of urine showed only small variations on successive days.

Method.—The daily 17-ketosteroid output of each man was determined from two successive 24-hour samples to provide a base-line, and at the end of the second collection testosterone proprionate, 100 mg. dissolved in 2·0 ml. of oil ('Perandren'), was injected into the left deltoid muscle. 24-hour samples of urine were collected for the next 72 hours, by the end of which time the urinary excretion of 17-ketosteroids had fallen to within a few milligrammes of the control levels. The excess output of 17-ketosteroids during the post-injection period was determined by subtracting the mean value for the two control days from the 24-hour output on each of the three post-injection days. The total excess of 17-ketosteroids excreted in the post-injection period, which may also be regarded as the percentage of the injected testosterone recovered as 17-ketosteroids is shown for each man, together with the control value, in the accompanying table.

OUTPUT OF 17-KETOSTEROIDS BEFORE AND AFTER INJECTION OF TESTOSTERONE IN EUROPEANS AND AFRICANS

Subject	Europeans		Africans	
	Control mean 17-ks/24 hr. (mg.)	Total excess 17-ks after testosterone (mg.)	Control mean 17-ks/24 hr. (mg.)	Total excess 17-ks after testosterone (mg.)
1	20·45	38·65	13·88	46·76
2	20·11	38·17	12·00	40·90
3	19·08	35·21	10·60	22·30
4	17·00	28·60	10·25	37·75
5	15·65	38·45	9·22	46·94
6	11·32	44·87	5·85	32·45
7	10·25	45·88	3·75	23·45
Mean	16·27	38·55	9·36	35·79

Results.—The mean values for the recovery of testosterone are not significantly different for the African and European groups, although the means for the control period show the same order of difference as we have already demonstrated on a larger sample. Recoveries of 35–40% are comparable to the values reported by other workers in similar tests in normal people. There seems to be no evidence of correlation between the daily 17-ketosteroid output of an individual and his ability to convert testosterone to 17-ketosteroid, as Engstrom et al. (1951) have also noted. These results, though few, lend no support to the view that the differences in daily 17-ketosteroid excretion between Africans and Europeans are due to defective conversion of at least the testicular precursors in Africans. It must be emphasised, however, that although about a third of the normal urinary 17-ketosteroids may be derived from testosterone produced by the testis, the exact nature of the precursors and the metabolic pathways involved in the formation of the remaining fraction are still far from clear.

If chronic disease were an important factor in producing the difference we have described, it might perhaps have been expected that the sample of African labourers would show a lower daily 17-ketosteroid output than the London students, and that any abnormalities in the response to testosterone would be most likely to be revealed in them; but, in fact, the Oshodi sample covers practically the entire range of daily 17-ketosteroid output seen in the African sample as a whole. It may well be, however, that liability to nutritional deficiency and to other diseases does not show the same socio-economic distribution in West Africa as it does in Europe.

One of us (D. W.) is now collecting data on the daily 17-ketosteroid excretion of African women, and their urine is being subjected to chromatography in the hope that more light will be shed on the origin of the low African output of 17-ketosteroid reported here.

We wish to thank Dr. F. L. Warren, under whose guidance many of the 17-ketosteroid assays were initially made, for his advice on many points; Dr. W. S. S. Ladell for his hospitality to one of us (N. A. B.) while working in the Hot Climate Physiological Research Unit, Oshodi, under a grant from the Colonial Medical Research Council; and Prof.

Alexander Brown, of University College, Ibadan, for obtaining some specimens for us. Messrs. Ciba supplied the perandren used in these experiments.

REFERENCES

Bjerneboe, M., Hamburger, C., Jersild, M. (1950) *Acta med. scand.* 136, 287.
Callow, N. H., Callow, R. K., Emmens, C. W. (1938) *Biochem. J.* 32, 1312.
Engstrom, W. W., Munson, P. L., Cook, L., Costa, P. J. (1951) *J. clin. Endocrinol.* 11, 416.
Forbes, A. P., Donaldson, E. C., Reifenstein, E. C. jun., Albright, F. (1947) *Ibid*, 7, 264.
Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, H., Reifenstein, E. C. jun. (1941) *Ibid*, 1, 234.
Hamburger, C. (1948) *Acta endocrinol.* 1, 19.
Kenigsberg, S., Pearson, S., McGavack, T. H. (1949) *J. clin. Endocrinol.* 9, 426.
Mason, H. L., Engstrom W. W. (1950) *Physiol. Rev.* 30, 321,
Robinson, A. M. (1948) *Brit. J. Cancer*, 2, 13.
Rupp, J., Cantarow, A., Rakoff, A. E., Paschkis, K. E. (1951) *J. clin. Endocrinol.* 11, 688.
Warren, F. L. (1950) *In* Potter, V. R., Methods in Medical Research. Chicago; vol. II, p. 314.
West, C. D., Tyler, J. H., Brown, H., Samuels, L. T. (1951) *J. clin. Endocrinol.* 11, 897.

FUNCTIONAL DISORDERS OF SMALL BOWEL AFTER GASTRECTOMY AND VAGOTOMY

CORRELATION OF RADIOGRAPHIC AND KYMOGRAPHIC STUDIES

A. J. GLAZEBROOK
M.D. Lond., M.R.C.P.E.

From Ministry of Pensions Hospital, Chapel Allerton, Leeds, and the Department of Surgery, University of Liverpool

> "It was in my mouth sweet as honey: and when I had eaten it, my belly was made bitter."—*Revelation* X, 10.

PARTIAL gastrectomy is accepted today as a major contribution to the therapy of peptic ulcer, and no really practicable alternative can be offered to the patient with a well-established penetrating and sclerotic lesion. It is a pity that post-gastrectomy syndromes occur and can at times be so incapacitating.

That these syndromes are ascribed largely to neurosis is not surprising, in view of the rooted belief that peptic ulcer is an organic manifestation of this or that type of personality. The simpler explanation—that the peptic ulcer or underlying intestinal dysfunction is the cause of both the psychic and somatic manifestations of the illness—has not yet gained universal acceptance.

After all, it is human for the surgeon to feel that the patient who complains after operation without obvious cause is being unreasonable. And yet partial gastrectomy and vagotomy are major mutilations of the alimentary tract, and when both are done in one person it is remarkable that serious complications are not more common.

I fancy, however, that they are more common than many surgeons would have us believe. Nearly a third of the patients in my gastric wards are suffering from one or other of the many postoperative syndromes, and their management has presented a difficult and well-nigh intractable problem, because some of them are worse off than they were before operation.

Some post-gastrectomy syndromes are now well recognised—the stomal ulcer, gastritis of the gastric stump, afferent-loop-distension vomiting, and late hypoglycæmic manifestations. Here I am concerned only with the long-term effect of gastrectomy and vagotomy on the function of the small bowel.

Machella (1950) thought the postprandial post-gastrectomy syndrome was associated with jejunal dilatation, but Glazebrook and Welbourn, in trying to confirm his observations, found jejunal spasm a prominent feature of the clinical picture (Welbourn 1951). Using the same methods again—namely, kymography and dextrose-barium-meal radiography—further cases have been investigated, and it now seems that at least three distinct functional disturbances of the small bowel may be found after gastrectomy and vagotomy.

METHODS

Intrajejunal Balloon Kymography.—A Miller-Abbott tube with attached balloon is swallowed under X-ray visualisation until the balloon lies within the efferent jejunal loop. The balloon is then distended with 20 ml. of air and its rubber tube attached to a tambour and thus to a lever writing on smoked paper.

Dextrose-barium Meal.—Dextrose was originally mixed with the barium in an attempt to confirm the work of Machella. It has since been realised that by increasing the intestinal gradient it emphasises the peristaltic function of the gut and is far more likely to reveal defects in the transport of a bolus than the ordinary meal. Trial and error showed that the best mixture for the purpose was 8 oz. of a 50% dextrose solution mixed with 8 oz. of barium. More sugar was liable to cause violent symptoms culminating in vomiting or collapse; less was of little diagnostic value.

When a postprandial syndrome is due to small-gut dysfunction, this dextrose-barium meal almost always reproduces the exact symptoms of which the patient complains; whereas, if some other condition, such as stomal ulcer, is present, nothing beyond

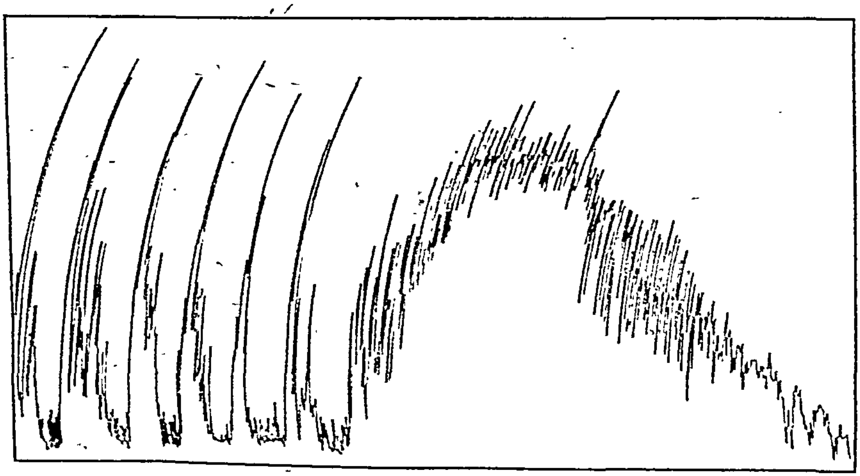


Fig 1—Kymographic tracing of "normal" efferent jejunal loop, in a patient with no symptoms after gastrectomy, showing broad-based long L waves on the left, and spasm caused by dromoran on the right.

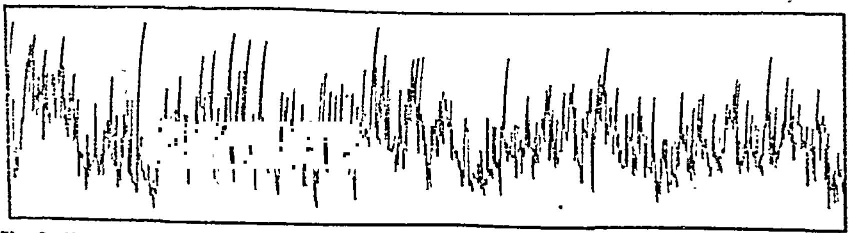


Fig. 2—Kymographic tracing in intestinal torpor (case 1), showing absence of L waves (cf. fig. 1).

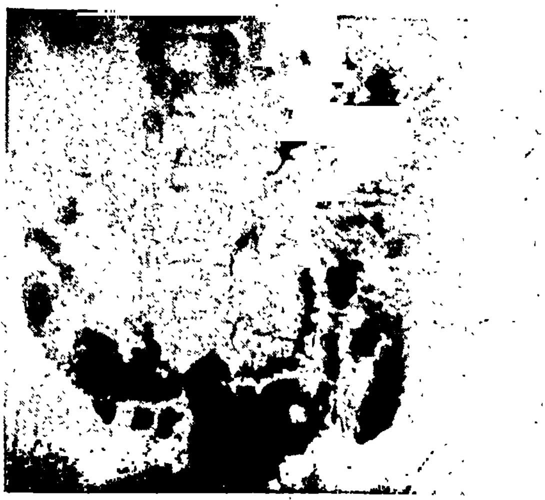


Fig. 3—Intestinal torpor (case 1), showing gross dilatation of jejunal coils, with barium clinging to coarse folds of gut wall.

that elicited by the ordinary barium meal, such as tenderness and after-pain over the stoma, is to be observed. This difference is a valuable diagnostic aid.

For the purpose of correlating the barium-meal picture with the kymographic tracings, the film taken 15 minutes after the ingestion of the whole of the mixture was found of most value.

"NORMAL" KYMOGRAPHIC TRACINGS

Chapman and Palazzo (1949) investigated the meaning of intestinal kymographic tracings by a technique which permitted simultaneous X-ray observation. On the whole, they confirmed the suggestions made by Ingelfinger and Abbott (1940), who first studied such tracings, regarding the nature of the L and S waves. They also described "spasms."

L waves are large, arrhythmic, and broadly based. They are nearly always associated with forward movement of the balloon, and thus represent peristaltic contractions.

S waves are small and of rapid frequency. They can be seen in a resting bowel, do not represent caudal movement of the balloon, and are considered to represent segmental ring-like non-propulsive contractions.

"*Spasms*" are elevation of the base-line usually to the upper limits of previous contractions, with superimposed small frequent segmental types of contraction. Caudal movement of the balloon ceases during a spasm.

The apparatus I have used is slightly less elaborate than that of Chapman and Palazzo (1949), and the pattern of kymographic tracing obtained in people who do not complain of any symptoms after gastrectomy, and therefore presumably have a "normal" efferent jejunal loop, is shown in fig. 1. On the left of the figure broad-based long L waves are seen; and, while these are being written, the patient feels a definite "tug downwards" of the balloon; that they are clearly associated with active peristalsis is shown by the travel of the balloon. Between the L waves are small frequent waves which may be due to segmental non-propulsive movements of the intestine but which I have found very hard to distinguish from respiratory movement. On the right is an artificial spasm produced by the injection of 'Dromoran'; I have not seen any movement of the balloon during such a spasm.

ABNORMAL KYMOGRAPHIC TRACINGS

On theoretical grounds variations from the normal might occur in peristaltic, segmental, or tonic activity. With regard to peristalsis, such variations could show an increase or decrease in the height of the L waves, or changes in their frequency. Similar considerations apply to segmental waves and tone, and probably many variants could be recorded, if a method less crude than a balloon-and-tambour system was devised. However, it has been found possible to recognise three well-differentiated types of tracings, and the following are illustrative cases:

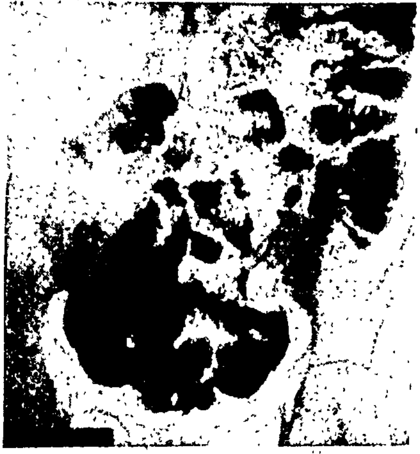


Fig. 5—Intestinal hurry (case 2): in 15 minutes barium had practically left stomach and jejunum and was entering cæcum.

Intestinal Torpor

Case 1.—A man, aged 30, had a peptic ulcer which made itself suddenly known by perforating in 1945. He was investigated and considered to have a hypertrophic gastritis with a duodenal ulcer. In 1946 partial gastrectomy was done, and at operation he was found to have two active duodenal ulcers and the scars of two gastric ulcers. After partial gastrectomy he suffered severely from painful indigestion and was thought to have a stomal ulcer. Laparotomy was undertaken in 1947 and, although no stomal ulcer was found, vagotomy was carried out. The vagotomy made no improvement in his condition. As nothing unusual was found at the second operation, neurosis as a basis for the illness had been strongly suspected. When he came under observation in 1951, his main complaints were of aching left-sided abdominal pain, coming on two or three times a day after food; progressive loss of weight, amounting to 3 st. in 4 years; obstinate constipation, his bowels moving once weekly in spite of purgatives; and anæmia. He was very depressed,

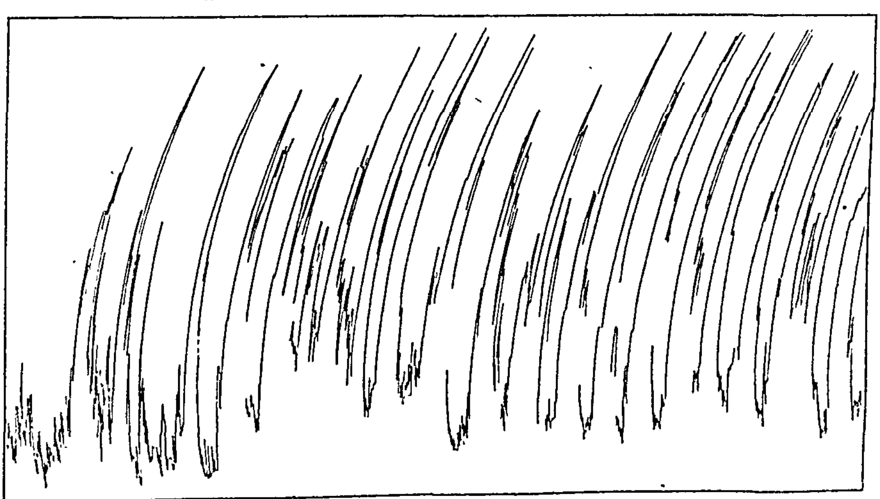


Fig. 4—Kymographic tracing in intestinal hurry (case 2), showing L waves. Balloon moved 20 in. caudally during this recording.

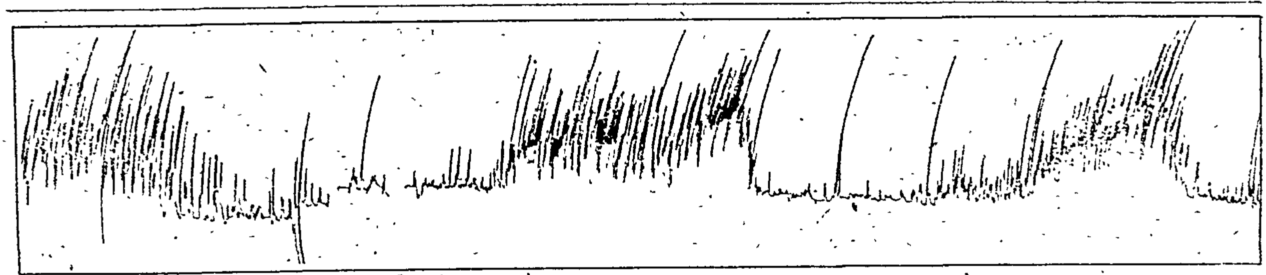


Fig. 6—Kymographic tracing in intestinal spasm (case 3).

being aware that he was now regarded as neurotic, if not a malingerer.

Kymography showed (fig. 2) a very low level of activity, with absence of the L waves seen in fig. 1, and there was practically no caudal movement of the balloon.

Radiography.—A dextrose-barium meal brought on the left-sided pain within 10 minutes, and the 15-minute film showed gross dilatation of the jejunal coils, with barium clinging to the great coarse folds of the gut wall (fig. 3).

Intestinal Hurry

Case 2.—A man, aged 39, had had vague indigestion for many years; duodenal ulcer was diagnosed in 1944, and partial gastrectomy was done for pyloric stenosis in 1946. Immediately after the operation he lost his appetite and began to have pain in the middle of his abdomen about 20 minutes after food, with palpitations, dampness of the palms, weakness of the legs, and a wish to lie down. Hot sweet drinks were particularly liable to bring on these symptoms. He lost 1 st. in weight during the next 4 years, and his bowels became rather looser than before, with putty-coloured stools.

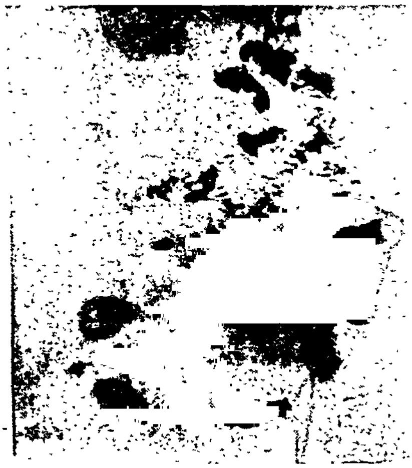


Fig. 7—Intestinal spasm (case 3), showing clumping of barium.

Kymography.—In striking contrast to case 1, the record consisted almost entirely of well-marked L waves (fig. 4), and the balloon travelled down the intestine at a great rate—50 inches in 2 hours.

Radiography.—A dextrose-barium meal brought on all the symptoms complained of, and in 15 minutes the barium had practically left the stomach and jejunum and was entering the cæcum (fig. 5).

Intestinal Spasm

Case 3.—A man, aged 31, had a duodenal ulcer which was first recognised in 1943. No major episodes, such as perforation and hæmatemesis had occurred, but he complained of particularly severe ulcer pain, and partial gastrectomy with vagotomy was done in 1950. Immediately after the operation the patient noticed a bloated full feeling in the midline below the navel, accompanied by a hot sweat, with palpitations, weakness, and a desire to lie down, persisting for an hour after the food. Subsequently he lost 2st. in weight, had obstinate constipation from time to time, lacked energy, felt weak on standing up suddenly, and for the last 6 weeks had had a sore tongue.

Kymography again showed a striking contrast to cases 1 and 2—a series of spasms, and there was no measurable movement of the balloon (fig. 6).

Radiography.—A dextrose-barium meal produced all the patient's postprandial symptoms, and the 15-minute film showed a curious clumping of the barium, the gut being tender over the empty parts, which were presumably in spasm (fig. 7).

OTHER KYMOGRAPHIC PATTERNS

These "pure" syndromes are not common. More often two or more of the fundamental disorders are found together:

Intestinal Spasm Followed by Intestinal Hurry

Case 4.—A man, aged 34. A duodenal ulcer had been suspected since 1940, although clear evidence of its presence was at first lacking. However, his symptoms were so severe and so characteristic that laparotomy was done in 1948, when no lesion of the stomach or of the duodenum was discovered and the abdomen was closed. Severe symptoms persisted after laparotomy, and early in 1950 radiography showed a juxtapyloric gastric ulcer. A partial gastrectomy allowed biopsy of the excised specimen, which confirmed the diagnosis. After this, severe symptoms, consisting in acute pain carrying on after meals and sited just above the navel, with sweating, palpitations, weakness, and a desire to lie down, persisted. The bowels became looser, the stools became larger and paler, and the patient lost 3 st. in weight in 18 months. So severe was the postprandial pain that he often induced vomiting to relieve it.

A stomal ulcer was diagnosed on clinical grounds, and another laparotomy was done. No evidence of stomal ulcer was found; nevertheless, vagotomy was performed. This made no difference to his symptoms.

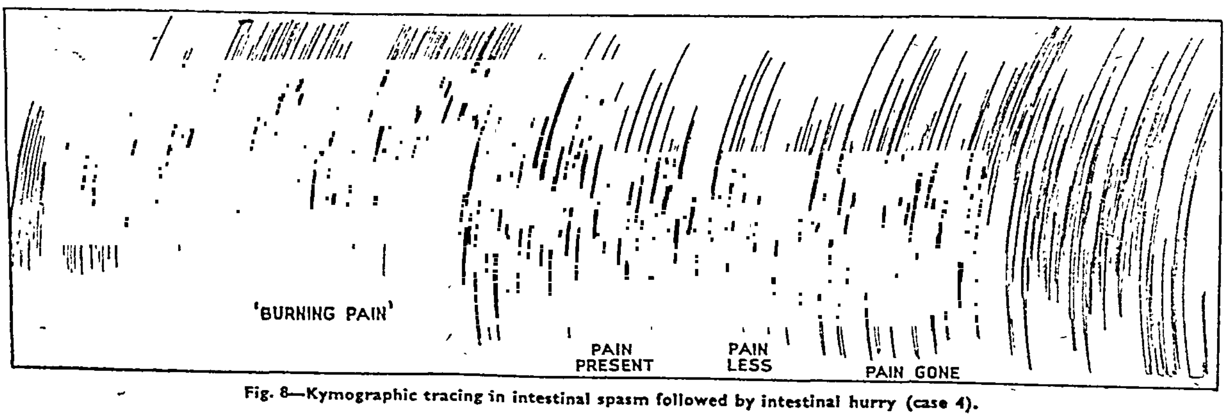


Fig. 8—Kymographic tracing in intestinal spasm followed by intestinal hurry (case 4).

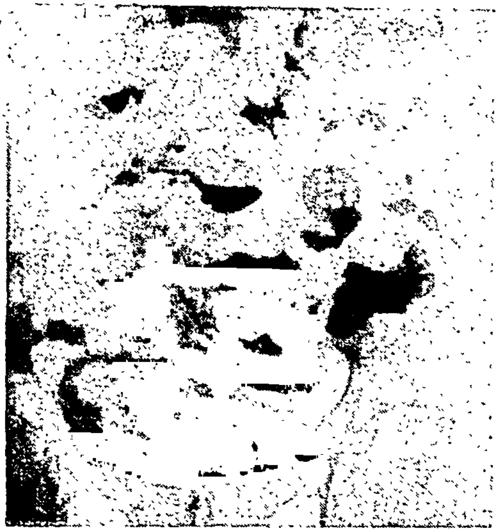


Fig. 9—Intestinal spasm followed by intestinal hurry (case 4).

Kymography showed a spasm, accompanied by a severe burning pain similar to that complained of after meals, which gradually tailed off into intestinal hurry with large frequent L waves, the pain at the same time disappearing (fig. 8).

Radiography.—A dextrose-barium meal reproduced the postprandial symptoms, and the 15-minute film is an excellent example of the appearance I have come to associate with intestinal spasm (fig. 9). When this patient was recalled an hour later for a further plate, he was discovered to be having diarrhœa, and he passed almost all the barium.

Intestinal Spasm Followed by Torpor

Case 5.—A man, aged 58, had had a duodenal ulcer for nearly 20 years. A *partial gastrectomy* was done in January, 1950, but after the operation he complained of colicky pains round the umbilicus after food, together with constipation.

Kymography in December, 1950, showed initial spasm tailing off into a rather incoördinated picture without definite L waves (fig. 10). The spasm was accompanied by the colicky pains complained of.

I chose this patient for demonstration of kymography to the Surgical Travellers Club in Liverpool in October, 1951. His symptoms of colic and constipation had disappeared at this time; he had no pain during the examination, and the record (fig. 11) approached "normal." He had had no special treatment.

DISCUSSION

The blowing up of balloons in men's insides does not seem likely to reproduce a naturally occurring state of affairs; and the addition of dextrose to their barium meals is perhaps a little unkind; possibly a cup of hot sweet tea would cause spasms and rushes of similar intensity. Also the material presented here is based on inpatient study of some fifty patients only. Hence too much must not be read into the results.

Nevertheless the issues raised are interesting. For instance, are these conditions the results of the operations, or are they primarily the causes of the illnesses for which the operations were done? Case 4 induces reflection.

What is the long-term effect of successful vagotomy on the functions of the small intestine? Is the torpor illustrated in fig. 2 the melancholy end-result? This might be expected, but in actual practice the severest examples of intestinal spasm are seen in vagotomised patients. Most of these, however, have had their vagotomy performed as a sequel to partial gastrectomy, because of persistent postprandial pain, stomal ulcer having been suspected but not found at operation. It is quite possible that spasm, not ulceration, was causing the pain, and that the vagotomy did nothing to relieve it. This view is supported by the fact that vagus-blocking agents may afford relief in the syndrome.

As regards treatment, it is clear that successful management of intestinal torpor, intestinal hurry, and intestinal spasm must be based on quite different principles.

Partial gastrectomy should be avoided unless there are definite surgical indications—among which I do not include "failure of medical treatment," where the criterion of failure is that the patient is apt to relapse once or twice a year. These patients should be strongly urged to await further advances in therapeutics rather than undergo operation. When post gastrectomy syndromes develop, vagal resection should not be lightly undertaken.

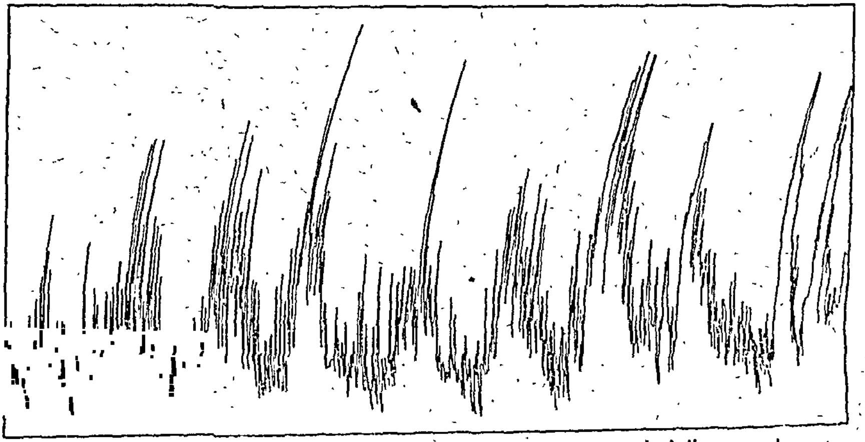


Fig. 11—"Normal" appearance in case 5 after his symptoms had disappeared.

SUMMARY

Intestinal motility has been studied in 50 patients with various abdominal symptoms after partial gastrec-

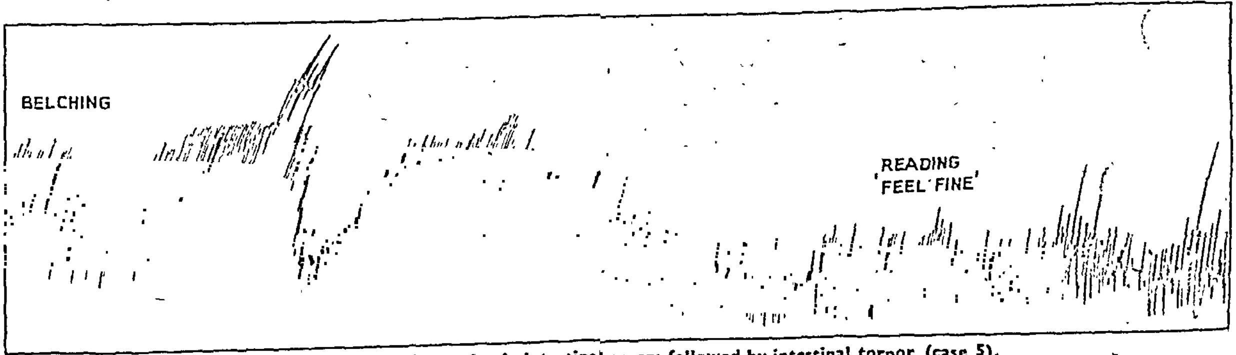


Fig. 10—Kymographic tracing in intestinal spasm followed by intestinal torpor (case 5).

tomy, with or without vagotomy. Intrajejunal balloon kymography and radiography after dextrose-barium meal have revealed main types of small-intestinal dysfunction, each of which may cause symptoms as follows:

1. *Intestinal Torpor.*—Constipation. with dull aching abdominal pains.

2. *Intestinal Hurry.*—" Dumping " symptoms after food (especially sweet, liquid, and bulky meals) frequent bulky pale stools; and loss of weight, sometimes progressive.

3. *Intestinal Spasm.*—Colicky abdominal pain (sometimes severe enough to suggest stomal ulcer) with or without " dumping " symptoms after food. Constipation.

Combinations of these motor disorders, such as spasm followed by hurry, or spasm followed by torpor, are more common than any type alone.

I am grateful to the Director-General of Medical Services, Ministry of Pensions, for permission to publish and for support and encouragement; and to Prof. C. A. Wells, in whose department much of this work was done.

REFERENCES

Chapman, W. P., Palazzo, W. L. (1949) *J. clin. Invest.* 28, 1517.
Ingelfinger, F. J., Abbott, W. O. (1949) *Amer. J. digest. Dis.* 7, 468.
Machella, T. E. (1950) *Gastroenterology*, 14, 237.
Welbourn, R. (1951) *Proc. R. Soc. Med.* 44, 773.

A DISINFECTANT BARRIER IN DRESSINGS APPLIED TO BURNS

E. J. L. LOWBURY
M.A., B.M. Oxfd

A. M. HOOD
F.I.M.L.T.

From the Medical Research Council Burns and Industrial Medicine Research Units, Birmingham Accident Hospital

DRESSINGS applied to burns often become soaked through with exudate, particularly during the first day or two after the burn is inflicted. Colebrook and Hood (1948), using a model wound, showed that pathogens may " grow through " dressings which are soaked with sterile plasma, and concluded that a burn may become infected in this way by organisms deposited on the outside of bandages. A burn may continue to produce exudate after the initial period if it is infected, and in this case the surface of a soaked dressing becomes a reservoir of pathogens from which infection may spread to other patients.

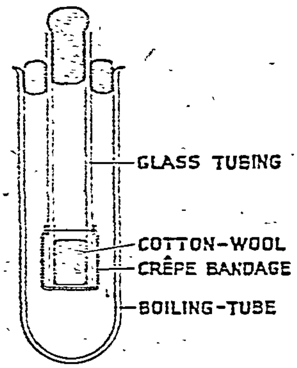
Plastics permeable to water vapour—e.g., ' Cellophane ' (Colebrook and Hood 1948) and ' Nylon ' derivatives (Bull et al. 1948)—can be used in some burns to prevent soaking through of dressings, but for burns in regions where the inclusion of such a layer is impracticable other methods of preventing the passage of bacteria through dressings are desirable.

The treatment of handkerchiefs with certain disinfectants by Dumbell and Lovelock (1949) suggested to us the trial of their methods on cotton-wool and on bandages used for the dressing of burns. In this paper we describe laboratory studies in which phenyl-mercuric bromide was shown to provide an effective barrier to the passage of common wound pathogens through experimental dressings soaked with sterile serum-broth. Phenyl-mercuric bromide was shown also to have a limited value as a disinfectant barrier when dry experimental dressings were soaked from one side with broth cultures of these bacteria.

MATERIALS AND METHODS

Model Wounds and Dressings

In most of the experiments the model wound and dressing consisted of a glass tube, ½ in. in diameter and about 3 in. long, plugged at one end with ½ in. of absorbent cotton-wool, over which four layers of crêpe bandage were firmly tied in contact with the cotton-wool (see figure). Cotton-wool or bandage impregnated with disinfectant were compared with unmedicated controls on these models, a number of replicates (generally 6) of each treated material and of the control material being set up with each organism at the same time. The model dressing was enclosed in a boiling-tube.



Small model dressing. Cotton-wool and crêpe bandage (inside boiling-tube) treated with disinfectants were compared with untreated control " dressings."

In some of the experiments the larger model wound described by Colebrook and Hood (1948) was used. This consisted of a brass tube 8 in. long and 2 in. in diameter with several holes bored in one side. Gauze wicks were passed through the holes, and the " limb " was dressed with layers of gauze, cotton-wool, and crêpe bandage. In separate experiments the outer layer of cotton-wool and the crêpe bandage were medicated with phenyl-mercuric bromide. Control tests with unmedicated cotton-wool and bandage were also made.

Impregnation of Dressings with Disinfectants

We selected for study a group of disinfectants which had been found effective in the medication of handkerchiefs (Dumbell and Lovelock 1949): phenyl-mercuric bromide, nitrate, and acetate, and octyl cresol.

Bandages and cotton-wool were treated with octyl cresol by soaking them in a solution of 4% octyl cresol in industrial spirit, and allowing the alcohol to evaporate. Phenyl-mercuric bromide was usually introduced by soaking bandages or cotton-wool in a 1 in 5 aqueous dilution of a 5% solution of phenyl-mercuric acetate in glacial acetic acid, and transferring, after wringing lightly, to a 5% solution of potassium bromide for fifteen minutes to precipitate phenyl-mercuric bromide. Bandages and cotton-wool were then washed in running cold water for five minutes (J. E. Lovelock, personal communication). They were allowed to dry in air at 37°C. In some experiments treated wool was autoclaved at 20 lb. for twenty minutes before use. Bandages were sometimes treated by soaking in a saturated solution of phenyl-mercuric bromide in alcohol. The nitrate and acetate were introduced from saturated solutions in distilled water and in alcohol. Attempts to use saturated aqueous solutions of phenyl-mercuric bromide were abandoned because of the low solubility of the salt in water (0·011% at 20°C).

Bacteria Used in Tests

One strain each of *Strep. pyogenes*, *Staph. aureus*, *Ps. pyocyanea*, *Proteus vulgaris*, and *Bact. aerogenes* were used. The staphylococcus was a strain of bacteriophage type 3A kindly supplied by the Staphylococcal Reference Laboratory. The other organisms had been isolated from burns.

Tests on Dressings Soaked with Sterile Serum-broth

Dressings were soaked with sterile 50% horse serum in nutrient broth by dropping it from a Pasteur pipette on to the inner surface of cotton-wool until the outer surface of the crêpe bandage was visibly moist. One drop of a twenty-four-hour broth culture of the test organism was then delivered on to the inner surface of the soaked cotton-wool. The tube, projecting through a cotton-wool plug into a large boiling-tube, was placed on its side in the incubator at 37°C, and the outer layer of the covering bandage was sampled with a moist swab after six hours and daily for a week. The bandage was also tested before swabbing for moisture by touching it with sterile filter-paper. If it was dry, sterile 50% serum-broth was added from the inside until moisture was apparent on the outside, and a drop of broth culture of the test organism was added.

TABLE I—PASSAGE OF ORGANISMS THROUGH DRESSINGS SOAKED WITH STERILE SERUM-BROTH

Organism	Experiments		Number of tubes in which organisms grew through dressings															
			Cotton-wool								Crêpe bandage							
—	Cotton-wool	Crêpe	Treated				Control				Treated				Control			
			+	−	Total	% +	+	−	Total	% +	+	−	Total	% +	+	−	Total	% +
Ps. pyocyanea ..	2	3	0	12	12	0	12	0	12	100	23	7	30	77	22	0	22	100
Pr. vulgaris ..	1	..	0	6	6	0	6	0	6	100	..	..	..	..	..	..	..	..
Bact. aerogenes ..	1	..	0	2	2	0	2	0	2	100	..	..	..	..	..	..	..	..
Strep. pyogenes ..	1	1	0	2	2	0	2	0	2	100	0	6	6	0	6	0	6	100
Staph. aureus ..	1	1	0	2	2	0	2	0	2	100	0	6	6	0	6	0	6	100

Swabs were inoculated on blood-agar, on cetrimide agar for *Ps. pyocyanea* (Lowbury 1951), and in 5 ml. amounts of nutrient broth, which were subcultured to solid media to exclude contamination when turbidity appeared after incubation.

These experiments, and a few made with the model "limb," were designed to study the possibility of preventing the passage of organisms through dressings already soaked by sterile exudate.

Experiments with Dry Dressings Soaked in Serum-broth Culture

In these experiments we dipped tubes with unsoaked dressings into beakers containing twenty-four-hour cultures of organisms in 50% serum-broth and allowed the dressing to become soaked with culture fluid. Tubes were left standing with the "dressing" submerged in the culture fluid. The inner surface of the cotton-wool was swabbed on the appearance of moisture, then every hour for six hours, and finally after eighteen hours' incubation at 37°C.

These experiments were designed to test the possibility of preventing the passage of bacteria through dry dressings when they became soaked with infected exudate.

RESULTS

Dressings Treated with Phenyl-mercuric Bromide

Small model dressings.—Table I shows that in the course of a week none of the organisms tested "grew through" treated cotton-wool which was kept moist with sterile serum-broth. In 6 experiments with *Ps. pyocyanea the treated* cotton-wool had been autoclaved. All the organisms grew through the control untreated cotton-wool in all the experiments.

Crêpe bandage treated with phenyl-mercuric bromide was found to prevent the passage of *Strep. pyogenes* and *Staph. aureus*, but results with *Ps. pyocyanea* were irregular, some specimens of treated crêpe being quite ineffective in preventing the passage of these organisms. In view of this finding, *the use of treated bandage for preventing the passage of Pr. vulgaris* and *Bact. aerogenes* was not studied.

Table II shows that, when dry cotton-wool, treated with phenyl-mercuric bromide, was moistened from the outside with serum-broth cultures of bacteria, all types of organism could be detected in samples taken from the inside of the cotton-wool dressing immediately after the appearance of moisture, and for periods ranging from one hour (*Ps. pyocyanea*) to six hours (*Proteus vulgaris* and *Bact. aerogenes*). After twenty-four hours, however, no organisms could be isolated from the inside of the dressings.

TABLE II—PASSAGE OF ORGANISMS THROUGH DRY DRESSINGS SOAKED WITH SERUM-BROTH CULTURE

Organism	Strains	Tubes	Organisms isolated from dressings after soaking							
			Immediate	Hours						
				1	2	3	4	5	6	24
Ps. pyocyanea	2	1	+	0	0	..	..	..	..	..
		2	+	+	0	..	..	..	..	..
Pr. vulgaris	1	1	+	+	+	+	+	+	+	0
		2	+	+	+	+	+	+	+	0
Bact. aerogenes	1	1	+	+	+	+	+	+	+	0
		2	+	+	+	+	+	+	+	0
Strep. pyogenes	1	1	±	±	0	0	0	0	0	0
Staph. aureus	1	1	+	±	±	0	0	0	0	0

Large model wound.—The results of an experiment with the large model wound agreed with those obtained with the small models in showing that cotton-wool treated with phenyl-mercuric bromide would prevent the passage of *Ps. pyocyanea* through dressings soaked with sterile serum-broth. In 4 out of 5 experiments with treated crêpe bandage *Ps. pyocyanea* did not "grow through" dressings soaked with sterile serum-broth.

Dressings Treated with Other Disinfectants

Octyl cresol.—*Ps. pyocyanea* was found to "grow through" dressings soaked with sterile serum-broth either when bandage (9/9 experiments) or cotton-wool and bandages (6/6 experiments) were medicated with octyl cresol. Organisms grew through treated bandages in 2/7 experiments with *Strep. pyogenes* and in 3/3 experiments with *Staph. aureus*.

Phenyl mercuric nitrate and acetate.—These did not provide a reliable disinfectant barrier in experiments with treated cotton-wool soaked with sterile serum-broth, 6 tubes being used for each compound.

Risk of Toxic Reaction to Disinfectant

Phenyl-mercuric salts have a low toxicity to animals (Weed and Ecker 1933), and the bromide is relatively insoluble in water. An experiment was made to find whether mercury could be detected in a model "wound" dressed with two layers of cotton-wool, the outer layer containing phenyl-mercuric bromide. The large model wound was used, sterile serum-broth being introduced from inside the tube to soak the layers of cotton-wool, and replenished daily to keep the dressing moist. Strips of gauze projecting through holes in the side of the tube were cut off daily and tested for mercury by the colour reaction with diphenyl carbazone (see Welcher 1947). No traces of mercury were detected in the gauze over a period of fourteen days.

DISCUSSION

When dressings become soaked through with exudate they no longer protect a burn from infection (Colebrook and Hood 1948). The outside of the bandage is contaminated with various organisms from the air and from contact with hands and with objects. In a study on the reservoirs of *Ps. pyocyanea* in burns wards this organism was isolated from the outside of about a third of the dry bandages covering burns, and from the hands of nearly half the nurses on duty (Lowbury 1952). Many skin-graft donor areas are found to be colonised by *Ps. pyocyanea* at the first dressing after operation, by which time the cotton-wool and bandage have usually become soaked through. It seems likely that these organisms "grow through" the dressing to contaminate the sterile operation wound.

The experiments described above show, in model wounds, that it may be possible to prevent the contamination of sterile burns through soaked dressings by using a layer of cotton-wool medicated with phenyl-mercuric bromide. A disinfectant barrier of this sort has the advantage over plastics, such as cellophane and nylon derivatives, that evaporation from the dressing is unimpeded, even in extensive burns, and that it could be used in regions—e.g., trunk and head—where the use of a plastic layer is difficult.

The value of such dressings as a barrier to the passage of organisms from an infected burn through soaked dressings is more doubtful. Although the bandage over a model dressing soaked with serum-broth cultures becomes sterile in twenty-four hours or less, this experiment probably underestimates the difficulties presented by a burn which continues to exude after the dressing has become soaked through.

Clinical studies are required before it can be decided whether the use of dressings treated with phenyl-mercuric bromide is practicable. In this unit dressings are replaced as soon as they become soaked through with exudate. However, in the event of a burning catastrophe, or in other circumstances in which dressings cannot be changed at short notice, it might be valuable to incorporate a disinfectant layer in the cover applied to burns as a routine.

SUMMARY

Cultures of *Ps. pyocyanea*, *Pr. vulgaris*, *Bact. aerogenes*, *Staph. aureus*, and *Strep. pyogenes* would not "grow through" model dressings soaked with sterile serum-broth when the cotton-wool was medicated with phenyl-mercuric bromide. The disinfectant was precipitated on to cotton-wool by addition of potassium bromide to a solution of phenyl-mercuric acetate in acetic acid, or occasionally by evaporation from an alcoholic solution of the compound.

Dry treated dressings dipped in serum-broth cultures did not prevent the passage of organisms, but the surface of the dressing became sterile in periods varying from one to six hours or within twenty-four hours.

The treatment of cotton-wool with octyl cresol and other phenyl-mercuric salts and the treatment of crêpe bandage with phenyl-mercuric bromide did not provide a reliable disinfectant barrier.

It is suggested that the infection of burns, which may occur when dressings become soaked through with exudate, might be prevented if a layer of treated cotton-wool is applied under the bandage.

We wish to thank Dr. Leonard Colebrook, F.R.S., Prof. J. R. Squire, and Dr. Elizabeth Topley for valuable advice and suggestions; Miss S. Baar for assistance; and British Drug Houses Ltd. for information about phenyl-mercuric bromide.

REFERENCES

Bull, J. P., Squire, J. R., Topley, E. (1948) *Lancet*, ii, 213.
Colebrook, L., Hood, A. M. (1948) *Ibid*, p. 682.
Dumbell, K. R., Lovelock, J. E. (1949) *Ibid*, i, 777.
Lowbury, E. J. L. (1951) *J. clin. Path.* 4, 66.
— (1952) In preparation.
Weed, L. A., Ecker, E. E. (1933) *J. infect. Dis.* 52, 354.
Welcher, F. J. (1947) Organic Analytic Reagents. New York; vol. III, p. 456.

"... Among ways not of explaining but of dealing with the irrational in man, the Greeks surely did well in giving rein to the Dionysiac and later the Corybantic cults. How much more enjoyable, socially effective and inexpensive their ecstatic orgies must have been than our shock treatments and other lonely, cold-blooded clinical devices."—JACQUETTA HAWKES. *The New Statesman and Nation*, April 19, 1952, p. 466.

OSTEOMYELITIS OF THE SKULL COMPLICATING ACUTE FRONTAL SINUSITIS

REPORT OF TWO CASES

W. L. THOMPSON
M.B. N.Z., F.R.C.S., D.L.O.
REGISTRAR

J. V. CLARK
F.R.C.S.E.
SURGEON

J. A. SIMONS
M.R.C.S.
SURGEON

EAR, NOSE, AND THROAT DEPARTMENT, KENT AND SUSSEX HOSPITAL, TUNBRIDGE WELLS

THE treatment of osteomyelitis of the skull complicating frontal sinusitis is still a subject of controversy. We do not claim originality for the method described in this paper, and we cannot yet say whether the cure was permanent. But we think that the treatment adopted is in keeping with accepted physiological principles and the pathology of this condition. Its threefold aim was drainage of the focus of infection, control of the pathological processes, and restoration of normal function.

PATHOLOGICAL CHANGES

Osteomyelitis of the cranial bones differs from that of other bones in that it is much more often secondary than primary. This is because the cranial bones do not possess the vascular epiphyses and metaphyses which are so commonly the seat of primary infection in the long bones.

The essential feature of the process is thrombophlebitis of the diploic veins. Inflammation begins in the diploë and usually spreads outwards; the sequestrum produced is therefore usually superficial. The inflammation may, however, spread inwards and give rise to an extradural or subdural abscess, meningitis, thrombophlebitis of the cranial sinuses, or a brain abscess.

As regards the frontal sinus, the veins of the mucosa are continuous with the large diploic veins of the frontal bone. The diploic veins, in turn, connect the veins of the scalp with all the blood sinuses. Hence infection of the frontal sinus, if accompanied by thrombophlebitis of the mucosal veins, may be followed by widespread osteomyelitis.

The infecting organisms are *Staphylococcus aureus*, most commonly, and the hæmolytic streptococcus. The condition is seen chiefly in young people, in whom the diploë is relatively larger than it is in later life.

Retrograde thrombosis in both the anterior frontal diploic veins and the extradural venous network probably explains the presence of isolated islands of osteomyelitis in advance of the main diseased area.

As the disease progresses, the macroscopic appearances of the bone are as follows:

(1) *Very early*: no visible change.
(2) *Next*: hyperæmia of the diploë.
(3) *Ten days later*: the bone softens, and the medullary spaces are full of pus and show granulations and thrombosis of their vessels.
(4) *Subsequently*: the bone changes in colour to red or black, with the formation of abscesses dissecting the periosteum or the dura mater from the bone.
(5) *Finally*: sequestration occurs.

CASE-RECORDS

Case 1.—A boy, aged 11 years, was admitted on March 20, 1951, with temperature 102°F and pulse-rate 120, complaining of discomfort and pain in the left eye for three days, swelling of the left eye and frontal headache for two days, and swelling of the right eye for one day. There was no history of a cold, nasal discharge, or sore throat. His previous health had been good.

On examination there was widespread and exquisitely tender pitting œdema of the entire scalp except over the occiput. The œdema also involved the upper half of the face, extending below the zygomatic arch on both sides, and was more severe on the left. The left eye was displaced downwards, forwards, and outwards, being fixed and completely closed by the œdematous lids. The conjunctiva was intensely congested. The right eye was also very œdematous, but not completely closed. The conjunctiva was suffused, but full movement of the eye was present, and there was no proptosis. The maximum tenderness was over the inner half of the anterior wall and floor of the left frontal sinus.

Anterior rhinoscopy revealed pus in the left middle meatus high up and anteriorly and also in the left olfactory cleft. The left middle turbinate was œdematous. There were no bony intranasal obstructions. Postnasal examination revealed pus on the left side above and below the middle turbinate.

Diagnosis.—Left pansinusitis with left subperiosteal orbital abscess and acute osteomyelitis of the skull.

Investigations.—A nasal swab and culture grew *Staph. aureus* sensitive to penicillin and streptomycin and resistant to chloramphenicol and sulphonamides. A blood-count showed white cells 7000 per c.mm. (neutrophils 61%, lymphocytes 27%, monocytes 12%), and hæmoglobin 80%.

Radiography did not reveal any disease of the bone in the region of the frontal sinuses. The left maxillary and ethmoid sinuses were completely opaque. The frontal sinuses were clear.

Treatment was immediately started with penicillin 250,000 units four-hourly and vasoconstrictors intranasally.

Forty-eight hours after admission the floor of the left frontal sinus was trephined. The usual external frontal incision was made, the subperiosteal orbital abscess was incised, releasing large quantities of pus, and the floor of the frontal sinus was opened just above the lacrimal groove. The frontal sinus was full of pus under pressure. The opening was enlarged sufficiently to allow inspection of the posterior wall of the sinus, which appeared intact. A tube drain was inserted into the sinus and brought out through the incision, which was closed. The left antrum was washed out at the same time, and yielded large quantities of pus. Penicillin and vasoconstrictors were continued as before.

Progress.—After the operation the patient's temperature dropped from 102°F to normal in forty-eight hours, and thereafter remained normal. The drainage tube was not removed until its discharge became mucoid on the fifth day after operation. The antra were washed out every four days until a clear return was obtained on the twelfth day after operation. Penicillin was continued in the same dosage for three weeks, after which 'Seclopen' 1 ml. daily was given until the patient was discharged two weeks later. The œdema of the scalp, eyes, and face slowly decreased but did not return to normal until two weeks after operation. The proptosis of the left eye persisted for three weeks, after which full movement and normal vision returned. Radiography of the skull and sinuses four weeks after operation showed only a thickened lining mucosa of the left antrum. No disease of the skull was seen.

The patient was discharged five weeks after admission, being then clinically normal, with wound cleanly healed and general condition good. Twelve months later there was no evidence of recurrence.

Case 2.—A boy, aged 17, was admitted on March 25, 1951, with temperature 105°F and pulse-rate 120, complaining of frontal headache for five days, swelling of the left eye for three days, swelling of the right eye for two days, and vomiting for twelve hours. There was a history of intermittent watery nasal discharge for six months before admission. This discharge was never purulent.

On examination there was extensive œdema of the entire scalp except the occiput, greater on the right side and extending down to the zygomatic arch on both sides. The maximum tenderness was over the inner half of the anterior wall and floor of the right frontal sinus. Both lids of both eyes were swollen, but the eyes were not completely closed. Full movement of both eyes was present and there was no proptosis. There was no neck rigidity, and Kernig's sign was negative. Anterior rhinoscopy revealed pus in both middle meatuses high up and anteriorly and in both olfactory clefts, worse on the left side. There was a high septal deviation to the right, compressing the right middle turbinate and partially concealing it. Post nasal examination showed pus on the left side only above and below the middle turbinate.

Diagnosis.—Acute pansinusitis with osteomyelitis of skull.

Investigations.—A nasal swab and culture grew *Staph. aureus* sensitive to penicillin, streptomycin, and chloramphenicol, and resistant to sulphonamides. A blood-count showed leucocytes 9000 per c.mm. (polymorphs 64%, lymphocytes 32%, monocytes 4%) and Hb 87%. Radiography of the skull and sinuses was omitted because the patient was too ill.

Immediate treatment was begun with intramuscular penicillin 250,000 units four-hourly and with vasoconstrictors intranasally.

Progress.—Twenty-four hours after admission the patient's temperature had dropped from 105° to 102°F and the œdema on the left side of the scalp had decreased considerably but at this stage the patient complained of intense right-sided headache and a sudden inability to move his right leg. Examination now revealed an incomplete flaccid flexor paralysis of the right leg and a right 6th-nerve paralysis. The fundi were normal. Lumbar puncture produced normal cerebrospinal fluid (C.S.F.) under normal pressure.

Thrombosis of the veins over the left motor cortical area was diagnosed.

Operation.—Forty-eight hours after admission the floor of the right frontal sinus was trephined. There was a moderate amount of pus in the frontal sinus but not under pressure. The mucosa was congested and polypoid. The posterior wall of the sinus appeared to be intact. A tube was inserted into the sinus and brought out through the external incision, which was closed. The right and left antra were washed out at the same time and yielded much pus. Penicillin and vasoconstrictors were continued as before.

Postoperative Progress.—On the day after operation the œdema of the left side of the scalp had subsided completely, and that of the right side had decreased slightly. The right leg remained paralysed. The temperature dropped to 100°F. On the second postoperative day the paralysis of the right leg became complete, and a mild weakness of the right arm developed. Lumbar puncture again showed normal C.S.F. at normal pressure. The eyes still showed no abnormalities except for the right 6th-nerve palsy, which persisted. On the third day there was some slight increase of power in the right leg. On the fourth day the patient had two epileptiform fits at an interval of an hour. The first was milder and subsided in ten minutes; the second was severe and was terminated after fifteen minutes by intravenous thiopentone. The fits were probably due to some extension of the venous thrombosis over the left motor cortex.

On the fifth postoperative day the patient was very much better. His temperature had fallen to normal. The œdema of the face had disappeared, and the right leg was considerably stronger. There was now a soft fluctuating area about 2 in. in diameter over the anterior part of the right parietal bone.

Convalescence was uneventful. The temperature remained normal. There were no further fits, and full power returned to the leg within ten days. The drainage tube was removed as soon as the discharge became mucoid (seventh postoperative day). Antral washouts were continued every four days until a clear return was obtained (sixteenth day after operation). Penicillin was continued in the same dosage for three weeks, after which seclopen was given for two weeks, at the end of which the patient was discharged. The soft fluctuant area in the right parietal region decreased until a circular depression, the size of a shilling, could readily be felt in this area two weeks after the operation. Thereafter the hole slowly decreased and two weeks later was no longer detectable. Radiography of the skull and sinuses four weeks after operation showed no evidence of any bony change or deficiency at the original site of the hole.

Five weeks after admission the patient was discharged, being clinically normal, with wound well healed and general condition good. Twelve months later there was no evidence of recurrence.

COMMENT

As already stated, it is too early to assess the final results because our patients may develop sequelæ later. But two facts seem to be clear: (1) these patients were nursed safely through a very critical period; and (2) the amount of bone work necessary in the future to deal with any residual infection is likely to be confined to a limited and circumscribed area.

It is interesting that in both cases a blood-count on the day of admission was within normal limits, and radiography (permissible only in case 1) revealed an apparently clear frontal sinus. In neither case were these facts in keeping with the clinical and operative findings.

We suggest that osteomyelitis of the skull complicating frontal sinusitis should be treated on the following lines:

(1) *Nasal Swab and Culture.*—Identification of the responsible organism and its sensitivity to the antibiotics and sulphonamides.

(2) *The effective antibiotic* should be given in large doses.

(3) *Early drainage of the responsible sinuses if ordinary drainage is inadequate.* Any surgical interference, however, should be as conservative as possible. Trephining of the floor of the frontal sinus allows inspection of the interior of the sinus and of its posterior wall.

(4) *Vasoconstrictors* intranasally, the maintenance of an *adequate nasal airway*, and *repeated antral washouts*, all with the object of aiding sinus drainage and restoring the normal physiological processes.

Residual disease can be dealt with at leisure after the acute phase has subsided.

RUPTURE OF THE TESTICLE

CHARLES DUNDON
M.Ch. N.U.I., F.R.C.S.

SENIOR REGISTRAR, ST. PETER'S HOSPITAL, LONDON; LATE REGISTRAR IN UROLOGY, ROYAL INFIRMARY, PRESTON, LANCS

BECAUSE of its mobility in the scrotum, the testicle is seldom ruptured by non-penetrating scrotal injuries.

A man, aged 49, was kicked in the scrotum during a fight in a public house. When he attended the casualty department eight hours later his scrotum was grossly swollen, and a diagnosis of bilateral hæmatoceles with a superficial hæmatoma was made. He had passed urine since the accident, and tests for hæmaturia were negative. His general condition was good.

Under general anæsthesia (Dr. B. Price) an incision was made over the left hæmatocele, and multiple clots were removed. There was a longitudinal rupture of the tunica albuginea, with protrusion of testicular tissue. The tunica was closed with interrupted catgut sutures. Another incision was made over the right hæmatocele. Many clots were removed, but the testicle presented only a minor contusion at the lower pole. A small corrugated rubber drain was inserted into each hæmatocele, and the wounds were closed with catgut sutures. Penicillin and sulphadimidine were given for seven days. Convalescence was uneventful, and the patient was discharged on the tenth day.

Seven months later the left testicle was of normal size and possessed normal testicular sensation.

Receus (1895) made the dogmatic statement that a ruptured testicle which was sutured and not removed always atrophied within six weeks. Likewise Guiteras (1912) said that whenever the tunica albuginea was ruptured the testicle eventually atrophied.

The rarity of rupture of the testicles is attributed to their mobility and rounded form and to the suppleness of the tissues surrounding them. Wesson (1946) states that it requires a force of 50 kg. to rupture a testicle. In his analysis of twelve reported cases, to which he added a thirteenth, McCrea (1951) found that the blow was directed upwards or obliquely upwards. Pain was the commonest immediate symptom, but shock was present in only three cases. The presenting sign was a gradually increasing swelling of the scrotum, hæmatocele was the usual preoperative diagnosis, and the testicle was removed in eight cases. But Campbell (1937) and Wesson (1946) reported cases in which, after suture of the tunica albuginea, the testis remained normal, and Counseller and Pratt (1944) described a similar case of suture, though they did not state the final result.

At the time of operation in the present case I thought that the testicle would atrophy. Now I believe that such a gloomy view is unwarranted, and I heartily recommend exposure and examination of the testicle in every case in which a hæmatocele follows trauma. If the testicle is ruptured, suture of the tunica albuginea should be attempted instead of orchidectomy.

I wish to thank Mr. W. H. Graham, F.R.C.S., consulting urologist to the Royal Infirmary, Preston, for permission to publish this case.

REFERENCES

Campbell, M. F. (1937) Pediatric Urology. New York and London.
Counseller, V. S., Pratt, J. H. jun. (1944) *J. Urol.* 52, 334.
Guiteras, R. (1912) Urology. New York and London.
McCrea, L. E. (1951) *J. Urol.* 66, 270.
Receus (1895) *Ann. Mal. Org. gén.-urin.* 13, 373.
Wesson, M. B. (1946) *Urol. cutan. Rev.* 50, 16.

Preliminary Communication

A "NEW" BLOOD-GROUP CHARACTER RELATED TO THE ABO SYSTEM

Two examples of blood possessing a hitherto unrecognised blood-group character related to the ABO system were found within the space of a few weeks in the department of pathology and bacteriology of the Seth Gordhandas Sunderdas Medical College, Bombay. Patient X was involved in a railway accident; patient Y was admitted with a stab wound in the abdomen. Both patients needed transfusion and both were apparently group O, but the serum of each agglutinated the red cells of 35 group-O Indian donors available for the direct compatibility test. Subsequently 80 more Indian group-O red-cell samples were tested with the same result. Plasma and not blood was therefore transfused.

A third example was subsequently found in the blood of a donor, Z, presenting himself for his first donation; this was the result of a deliberate search. None of these three men, all of whom are Indians, had been previously transfused.

The serum from each of these three men was found to contain anti-A, anti-A_1, anti-B, and anti-H, antibodies which account for the agglutination of red cells of all "ordinary" ABO groups. So far the only red cells not agglutinated by these three sera are those of the three men from whom the sera came.

These are by far the most powerful examples of human anti-H so far reported; they are also the first examples to come from persons superficially belonging to group O. It should be said that there are two types of antibody which agglutinate O and A_2 cells preferentially: one of them can be inhibited by secretor saliva and is called anti-H; and the other is not inhibited and is called anti-O.[1] There is considerable evidence, however, that not all sera classified as anti-O are of the same specificity, and it is not known which, if any, of these sera react specifically with the product of Bernstein's O gene.

The following evidence for the identity of the anti-H agglutinin relates for simplicity to the serum of patient X, which was the more exhaustively investigated, though all the critical tests were applied also to the serum of Y and to that of Z.

The serum was titrated against the red cells of 37 group-O English people selected to reveal the presence of the following antibodies, or mixtures thereof: anti-M, –N, –S, –s, anti-P, anti-C, –c, –C^w, –D, –d, –E, –e, anti-Lu^a, anti-K, –k, anti-Le^a, –Le^b, anti-Fy^a,

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[1] Morgan, W. T. J., Watkins, W. M. *Brit. J. exp. Path.* 1948, 29, 159.

—Fy^b, and anti-Jk^a. The fact that all the cell samples were agglutinated to the same degree (antibody titre 128–256) strongly suggested that we were dealing with a single antibody which was not one of the above; this was further supported by the observation that the degree of agglutination was the same whether the tests were done at 37°C, 24°C, 12°C, or 5°C. The insensitivity to change of temperature is an unusual finding; it was shown also by the anti-A, anti-A_1, and anti-B in the serum.

The antibody agglutinating O cells was inhibited by saliva from secretors belonging to all A_1 A_2 B O blood-groups, but it was not inhibited by saliva of non-secretors of these groups; the degree of inhibition was approximately parallel with the degree of inhibition of an eel anti-H serum caused by the same salivas.

Absorption of the serum by an equal volume of packed group-O red cells [Le(a+b−) and also Le(a−b+)] removed the anti-H, leaving the anti-A, anti-A_1, and anti-B unchanged. Absorption by A_1 cells [Le(a+b−) and Le(a−b+)], by B cells [Le(a+b−)] and by A_1B cells [Le(a−b+)] reduced the anti-H in varying degrees; the ability of the absorbing cells to remove anti-H roughly paralleled the reactivity of these cells with other anti-H and anti-O sera. The serum absorbed three times with an equal volume of A_1B Le(a−b+) cells contained a much weakened anti-H free from anti-A and anti-B. Six absorptions of the serum with the cells of donor Z left all the antibodies unchanged. Absorption with A_1 and B cells showed some cross-absorption of the heterologous antibodies anti-B and anti-A. There was some difficulty in showing that anti-A and anti-B were indeed present, although both antibodies were isolated after continued appropriate absorptions. Anti-A_1 was demonstrated in the serum after neutralisation of the anti-A, anti-B, and anti-H with A_1B saliva from a secretor.

TITRES OF ANTI-H, ANTI-A, ANTI-A_1, AND ANTI-B IN THE THREE SERA

Serum of	Test cells			
	O	A_2	A_1	B
X	256	512	2048	256
Y	256	512	1024	1024
Z	32	32	32	32

The titre of anti-H in the three sera is of the same order as that of the anti-A and the anti-B (see table).

The blood-groups of the three men are as follows:

Patient X.—"O," MN.Ss, P+, CDe/CDe, Lu(a−), K−, Le(a+b−), Fy(a+), Jk(a+), Tj(a+).

Patient Y.—"O," MsMs, P+, CDe/cde, Lu(a−), K−, Le(a+b−), Fy(a+), Jk(a+), Tj(a+).

Donor Z.—"O," MSMs, P+, CDe/CDe, Lu(a−), K−, Le(a+b−), Fy(a+), Jk(a+), Tj(a+).

None of the three men secretes A, B, H, or Le^b substance in his saliva; all three secrete Le^a substance.

The red cells of the three men were not agglutinated by 6 anti-A sera, nor by 4 anti-B sera, nor by 8 anti-A + anti-B (group O) sera; all these sera were selected for their high titre of antibody. The cells were not agglutinated by 11 human and animal (rabbit, cattle, eel, chicken, and goat) anti-H sera, nor by 23 human anti-O sera—i.e., the cells were not agglutinated to a greater degree than were A_1 B control cells. Control group-O cells sent from Bombay to London under the same conditions were found to react with all the anti-H and anti-O sera almost as strongly as fresh group-O control cells.

The red cells of the three men cannot be called group A, B, or AB. They can hardly be called group O, because they are not agglutinated by the types of antisera which agglutinate O blood particularly strongly. Further, in the serum of the three men is an antibody which agglutinates preferentially the red cells of group O; this antibody is powerful and active at 37°C and, so far as can be hazarded from three cases, appears regularly when its equivalent antigen is absent from the red cells. This regular appearance is peculiar to anti-A and anti-B, and suggests that the antibody belongs to the fundamental ABO system.

The men may be homozygous for a "new" allelomorph at the A_1 A_2 B O locus. The probability that they are homozygous was somewhat strengthened when inquiry revealed that the parents of patient X are first cousins; the parents of the other two men are not known to be related to each other, or to patient X. A "new" allelomorph of the A_1 A_2 B O locus appears to be the easiest explanation within the classical framework of the ABO groups.

The facts will, however, fit a recent modification (Morgan and Watkins[1]) of the theory of Hirzsfeld and Amzel.[2] H is considered a basic blood-group character which is changed by a variety of mutant genes in steps towards A, B, or O, and a final step to complete A_c, B_c, or O_c is pictured. The three men could be O_cO_c, and the theory would allow their serum to contain anti-H. This would, however, mean that the antisera at present called anti-O are not acting on the product of Bernstein's O gene; which would not be surprising in view of unpublished observations of two of us (W. T. J. M. and W. M. W.) on the reactivity of anti-O sera with cells of known genotypes. Further, there has been a recent suggestion by Sanger[3] that anti-H and anti-O may be antibodies of the same general specificity, the one occurring in non-secretor and the other in secretor persons.

The true explanation will have to await new facts. Circumstances have so far prevented genetical investigations, but it is hoped that relatives of at least one of these three men will be available. However, this preliminary account may encourage transfusion services, especially in India, to test the serum of all donors against group-O red cells. This "new" allelomorph may not be very uncommon in India; once the blood of the two patients had drawn attention to the "new" group, the third example was found in a systematic examination of blood from 160 donors. To our knowledge no such blood has been noted in Europe or the United States, though millions of appropriate tests must have been made.

SUMMARY

Three examples of Indian blood possessing a "new" blood-group character related to the ABO system have been found in Bombay.

The red cells of the three persons studied are not agglutinated by anti-A, anti-A_1, anti-B, anti-H, or anti-O sera. The serum of each contains anti-A, anti-A_1, anti-B, and anti-H; the only cells so far tested which are not agglutinated are those of the donors of these three sera.

Department of Pathology and Bacteriology, Seth Gordhandas Sunderdas Medical College, Bombay

Y. M. BHENDE
M.D. Bombay
C. K. DESHPANDE
M.B. Bombay
H. M. BHATIA
B.Sc. Bombay

Medical Research Council Blood Group Research Unit, Lister Institute of Preventive Medicine, London

RUTH SANGER
Ph.D. Lond., B.Sc. Sydney
R. R. RACE
Ph.D. Camb., M.R.C.S., F.R.S.

Lister Institute of Preventive Medicine, London

W. T. J. MORGAN
Ph.D., D.Sc. Lond., D.Sc. Zürich, F.R.S.
WINIFRED M. WATKINS
Ph.D., B.Sc. Lond.

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[2] Hirzsfeld, L., Amzel, R. *Ann. Inst. Pasteur*, 1940, 65, 251.
[3] Sanger, R. *Nature, Lond.* 1952 (in the press).

Medical Societies

ROYAL SOCIETY OF MEDICINE

Health: Its Study and Culture

The section of epidemiology and State medicine of the Royal Society of Medicine met on March 21, under the chairmanship of Dr. W. H. Bradley, to discuss Health—Its Study and Culture in the Nation Today.

Sir **Alan Rook** referred to the shortcomings of the National Health Service whereby preventive medicine, the only form which could be claimed to pay a dividend in any real sense, has been ignominiously relegated to the background; at present out of every £10 spent on the health services a mere 3*s.* is allocated to specifically preventive work, and the medical officer of health and his auxiliaries now gaze impotently on the wreckage of a laboriously constructed organisation which has served as a model to the world. Meanwhile much food is dirty even when prepared in our best factories and hotels; the personal hygiene of school-children and Service recruits leaves much to be desired; and ill health, especially mental ill health, appears to be on the increase. Even amongst university students, who are favourably placed as regards education and environment, tuberculosis and mental disease compete for first place as causes of serious illness.

It is clear that the acquisition and maintenance of sound health depend on complex factors, and no ready definition of the normal is available. A standard of physical health satisfactory for a city office worker could not be expected to fit one for an expedition to Mount Everest. In like manner, mental health and intelligence tests must be related to the background of the subjects tested, while the normality of those who apply the tests should be beyond suspicion. Assessment of social health is inevitably beset with difficulties; an oblique approach, by study of individuals and groups at work and play under ordinary conditions and their reactions to situations of stress, is more likely to bear fruit than direct observation under test conditions. It is important that our health propaganda, especially in connection with the early recognition of ill health and disease, should not make us unduly disease-conscious and convert us into a race of hypochondriacs.

Dr. **T. A. Lloyd-Davies** confined himself largely to industrial health problems. The vulnerability of adolescents of each sex to the stresses of modern industrial and commercial life and work makes them more absence-prone and accident-prone than older people, who have been found to be more stable emotionally, economically, and socially. Personnel selection with the declared aim of getting each individual into the right job has serious limitations in a predominantly machine-governed age, which finds only mass-production methods effective and profitable; the majority work only for the money and the freedom it brings, finding little real satisfaction in their job. It is impossible to view the future without misgiving, despite widespread sustained efforts towards cultural, economic, and social amelioration.

Major **M. M. Lewis** affirmed the value of the PULHEEMS system of classification and assessment in the Army, and felt that further improvements in this direction are on the way. The Services provide an excellent opportunity for intensive study of healthy adults under conditions which can be controlled in a way unlikely ever to be possible with civilians except in totalitarian countries. Mental health, which depends largely on morale, directly influences physical health; and the reverse is also true, especially in relation to the psychoneuroses, which account for approximately one-third of the discharges from the Army on account of invalidity. This proportion could be reduced by suitable prophylactic measures, including sound administrative procedures, good man-management, and family welfare, as well as appropriate job-selection. Fruitful lines of study are the investigation of normal subjects and their reactions to different environments, intensive instruction in health education (especially mental health), and close liaison between psychologists, psychiatrists, and hygienists.

In opening the discussion, Dr. **W. P. Kennedy** remarked that the subject still lacks a basic discipline such as is found in the allied subject of pathology. Health and disease can be expressed in various ways according to one's viewpoint; but in simple terms they are the opposite poles of an unbroken line or continuum with at one end death and at the other optimum health, manifested in physical, mental, and spiritual well-being. This concept of the essential unity of health and disease is consistent with the holistic concept in biology and may prove of practical use in establishing a calculus of health.

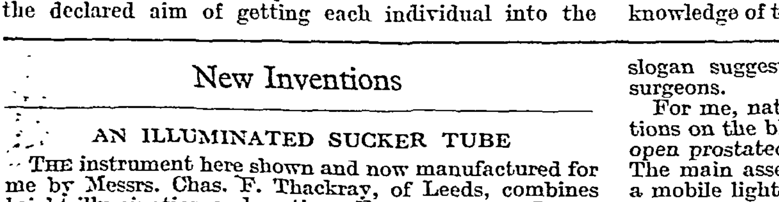
Dr. **N. H. Mackworth** offered practical suggestions for further study, including: (1) the effect of deprivation of sleep in producing minor deviations from normal health; (2) repeated observations on the same subjects, even on small groups (a more fruitful line than simple observations on large numbers); and (3) investigation of the capacity of individuals to rise to demands by virtue of incentives, and their failure through adverse circumstances such as lack of sleep or over-heated environment. The daily-performance measure suggested was the difference between activity, with and without the incentive of a progress record giving subjects full knowledge of their achievement in the current test session.

New Inventions

AN ILLUMINATED SUCKER TUBE

The instrument here shown and now manufactured for me by Messrs. Chas. F. Thackray, of Leeds, combines bright illumination and suction. For many years I used its prototype, which I made by tying in a rough but practicable way a Nitch's flexible bladder-lamp to a straight sucker tube (Ch. 24). The simplicity and utility of the instrument has induced me to publish my idea in the developed form. "Suck and see" was the slogan suggested by one of my more flippant house-surgeons.

For me, naturally, its greatest use has been in operations on the bladder base for removal of growths, and in open prostatectomy, whether transvesical or retropubic. The main asset is its aid in the arrest of hæmorrhage; a mobile light illuminating a suck-dried surface exposes the deepest bleeding points more effectively than does any fixed light, whether incorporated in a self-retaining retractor or from an external source. Especially is it useful to aid hæmostasis where bleeding is copious into the depth of a hypervascular prostatic bed. It should be noted that the lamp-holder slides in gripping supports welded to the sucker tube. The angle of the lamp-stem can be varied as required. The whole outfit, including electric-light connections and leads, can be boiled.



JOHN EVERIDGE
O.B.E., F.R.C.S.
Consulting Urological Surgeon,
King's College Hospital, London

Reviews of Books

The Apologie and Treatise of Ambroise Paré

Containing the Voyages made in Divers Places, with many of his Writings upon Surgery. Editor: GEOFFREY KEYNES, M.D., F.R.C.S. London: Falcon Educational Books. 1951. Pp. 227. 15*s.*

Ambroise Paré, universally recognised as one of the geniuses of surgery, is known to most of us as a great surgical craftsman whose becoming humility caused him to assign to God the credit for the many and surprising cures he wrought. This lively book, however, gives a very different picture; for surely no writer except Benvenuto Cellini (who, at the French court in 1537, probably met Paré) has so full-bloodedly and with such gusto extolled his own cleverness. At the same time he etched in the background of Renaissance Europe.

The son of a barber, and for years a barber-surgeon, Paré rose to eminence by sheer ability and personality, being sought after by the king and his nobles as a military surgeon, and exalted to the higher College of St. Côme by his colleagues and rivals. The *Apologie and Treatise* was written in reply to the dean of the Faculty of Physicians, Étienne Gourmelin, who had attacked Paré's scholarship because he published in French and not in Latin, the language of learning. And what a reply it is! A tale of arms and men, battles and sieges, faint pity and barbaric cruelty, through all of which passes Ambroise Paré, as actor, healing the wounded, and as observer, describing and commenting on events—all to shame and discomfit Gourmelin, "my little master," as he ironically calls him.

His wide interests and clear technical writing are shown in the dozen or so essays on medical subjects which comprise the second half of this book, ranging widely through the field of surgery, medicine, and metaphysics, and concluding with a dissertation on forensic medicine which might be read with benefit today. In the first part, Paré is consciously striving to show his prowess, and succeeds. In the second he writes as a scientist, seeking to advance the interests of his science without any motive of personal aggrandisement; and here, of course, he demonstrates his greatness even more effectively.

In the informative introduction Mr. Keynes acknowledges his indebtedness to Malgaigne who between 1806 and 1865 edited Paré's works and told of his life; but the text used is that of a folio printed by Th. Cotes and R. Young in 1634 "translated out of the Latine and compared with the French by Th. Johnson" (believed to have been a botanist and apothecary). It is thought that the more important part, the *Apologie and Treatise*, was taken by him from a direct translation from French published earlier by George Baker, a London surgeon. The book is produced with style and taste and is a joy to own. In Paré's words which conclude his *Apologie*: "I think there is not any man so ticklish, which taketh not in good part, what I have said, seeing my discourse is true and that the effect sheweth the thing to the eye, reason being my warrant against all Calumnie."

Obstetrical Practice

5th ed. ALFRED C. BECK, M.D., professor emeritus of obstetrics and gynecology, State of New York. London: Baillière, Tindall, & Cox. 1951. Pp. 1073 76*s.* 6*d.*

FIVE editions, two reprints, and two foreign editions in fifteen years speaks for the popularity of this book. The latest edition is virtually a new work, for much has been rewritten.

The first three chapters give an account of recent investigations into the development of the ovary, the menstrual cycle, and the early development of the ovum to which the Carnegie Institute has made important contributions. Goertler's conception of the arrangement of the uterine muscular fibres has displaced former ideas. Professor Beck attaches great importance to diet in pregnancy; and his views, based on observation and research, have a message for many countries, including Britain.

The book is fully up to date. No fewer than 390 of the illustrations have been redrawn. There is a full index and an extensive bibliography at the end of each chapter. Print is good, but perhaps the first signs of austerity are just visible in the quality of the paper. The book is rather lengthy for most students in this country, but it contains very little that would not be accepted as sound and sensible in most teaching centres.

Medical Disorders of the Locomotor System

Including the Rheumatic Diseases. 2nd. ed. ERNEST FLETCHER, M.A., M.D. Camb., M.R.C.P., physician in charge of the department of rheumatism and lecturer on the rheumatic diseases, Royal Free Hospital, London. Edinburgh: E. & S. Livingstone. 1951. Pp. 884. 60*s.*

A COMMITTEE of the Royal College of Physicians recently expressed the view that the chronic rheumatic diseases ought to have greater attention within the scope of general medicine, and recommended that in each of the hospital regions at least one special centre should be set up to undertake organised treatment, teaching, and research on these conditions. The rheumatic diseases would thus be in the same position as gastro-enterology, cardiology, and neurology—subjects which are established as meriting special training yet which remain part of general medicine.

Dr. Ernest Fletcher dislikes the term rheumatology and prefers to call the specialty "the study of the medical disorders of the locomotor system." This symposium, which he edits and to which he contributes a large part, was first published in 1947, and has been widely known and valued as a work of reference. In the new edition he provides an up-to-date appendix collating the available experience on treatment of rheumatic and other diseases with cortisone and A.C.T.H. Other new sections deal with pain, bone physiology and pathology, collagen diseases, and psychiatry in relation to locomotor disorders. Outstanding among new contributions are those of Prof. S. L. Baker on bone physiology and pathology, and Dr. H. J. Gibson on laboratory findings. There is very little overlapping, and in the treatment sections Dr. Fletcher and his associates always make it clear which methods have not been put to the test of their own practical experience.

The Hair and Scalp (4th ed. London: Edward Arnold. 1952. Pp. 316. 25*s.*).—For nearly twenty years Dr. Agnes Savill's book has been accepted as a standard work. Despite the efficient help of distinguished collaborators, it is largely an expression of personal beliefs, based on experience and on careful study of the writings of others. It reads well, and contains much useful information not easily obtained elsewhere; but it is vulnerable because the writer has nailed her flag to Sabouraud's mast and makes no attempt to mollify readers educated in a later and more critical period. Though it is designed to be of use to general practitioners and others, it can usefully be read by the young dermatologist, for the gist of many chapters may be memorised with advantage and the information given in others should sharpen the critical faculties.

A Textbook of Clinical Neurology (3rd ed. London: Cassell. 1951. Pp. 709. 75*s.*).—This edition of Prof. J. M. Nielsen's textbook carries news of recent advances in the specialty, including new views on the ætiology and treatment of polyneuritis, based on work with dimercaprol, and on recognition of the widespread occurrence of porphyria. The diagnosis of cerebral aneurysm has been reconsidered in the light of the latest developments in angiography; the chapters on epilepsy, poliomyelitis, and syphilis of the nervous system have been rewritten; and there are new chapters on multiple sclerosis and on the psychoneuroses. The glossy paper reproduces admirably the many fine photographs and diagrams which make this book such a pleasure to examine. The arrangement of the subject (from below upwards, anatomically) still seems to us to complicate rather than simplify clinical neurology, but it is always refreshing to a reader to approach his subject by a new route, and the popularity of the work is evidence that many find this road as convenient to travel as any.

THE LANCET

LONDON: SATURDAY, MAY 3, 1952

Clinical Research

MEDICAL research in this country is sponsored by the Medical Research Council, the universities, medical trusts, and commercial drug houses, and under the National Health Service. Probably no public money is used more effectively than that allotted to the Medical Research Council; but in the council's work the emphasis is much more on fundamental studies than on simple problems concerning the clinician, and much the same is true of research in the university departments and by commercial firms. In regional hospitals under the National Health Service there is undoubtedly much scope for simple clinical research, with special reference to the results of treatment and the natural history of disease. The efficiency of the hospital services would be much enhanced if such research became as much a part of the consultant's duty as the routine care of patients. Speaking at the annual meeting of the United Sheffield Hospitals on April 17, Sir CECIL WAKELEY [1] declared:

> "There is a great tendency for the medical profession and the laity to think that clinical research can be carried out only in hospital, where modern equipment is at hand and every aid to diagnosis is provided. But this is very far from the truth. Let us consider for a moment what is meant by clinical research. It is the painstaking investigation of individuals in the course of treating and caring for patients; it leads to an accumulation of knowledge which may be invaluable in the prevention and treatment of disease and in the maintenance of health. This knowledge may aid the advance of the practice of medicine in any of its many branches. It may confirm or refute established practice. It may point the way to new discovery or treatment. The essence of clinical research is that it is carried out by a clinician—be he general practitioner or specialist."

The time is particularly opportune for promoting clinical research in peripheral hospitals. Since the late war many young consultants have taken part in research as ex-Service registrars, and have gained the attitude needed for a continued interest in investigation. Sir CECIL WAKELEY defines the necessary qualities as natural curiosity, capacity for hard work, determination to keep detailed notes, ability to observe, healthy scepticism, and a background of culture—a constellation of shining virtues probably by no means uncommon among consultants. Most large hospitals can satisfy the requirements for useful work. A well-organised records department is essential; but the importance of this is now widely recognised, and in many centres a records officer has been appointed. A diagnostic classification system is needed, and with local modifications the International Classification of Diseases is satisfactory. The records themselves must describe adequately the illness and investigations; but clinical research does not usually demand the extremely detailed records which are sometimes made in its name. There is no doubt, moreover, that well-planned proleptic observations are infinitely preferable to retrospective analysis from notes made by a succession of junior staff. A small but up-to-date medical library is needed, in order to keep in touch with work in other countries; and boards of governors and management committees seem to be willing to provide money for this purpose. Perhaps the biggest difficulty in regional hospitals is in finding time; but somehow only busy people have time to organise new ventures, and there is no reason why consultants should not take study leave now and again. Commonly some financial support will have to be found. Special clerical or technical assistance may be required; and often this can be had on a part-time basis—for example, from married women who have previously worked as doctors, radiographers, or medical secretaries. Special apparatus, too, may be needed. Financial support may come either from a local research fund of the sort mentioned by Dr. AVERY JONES in his letter on p. 922, or through a grant by a regional research committee (such committees have been set up in six of the regions). There is much to be said for providing small-scale financial support at the periphery rather than depending on central organisations. More ambitious programmes, particularly those needing full-time medical staff, should undoubtedly come under the supervision of an academic centre or the Medical Research Council. There is no shortage of money for medical research; but at present this is unevenly distributed, with very little going to the periphery. The formation of regional associations of physicians, surgeons, or other groups will undoubtedly encourage investigation; and as these associations become well established coöperative research will be organised within regions. A start in this direction has been made in the Oxford region with a study on ulcerative colitis under Prof. L. J. WITTS.

In his address Sir CECIL WAKELEY insisted that useful research could also be undertaken by general practitioners, and that the organisation of group practices would encourage such a development. Unfortunately undergraduate training does not encourage enterprise of this sort. The curriculum is essentially technological; and some think it admirably designed to inhibit original thought. There is, for instance, far less encouragement to look up original references than in other faculties. The writing of essays or commentaries, quoting original sources, which is the rule in arts faculties, normally has no place in the medical student's training, though in at least one provincial teaching centre it has proved popular and stimulating to both students and staff. Such a practice, however modestly pursued, would encourage the critical faculty of future doctors; and in a few it would initiate a life-long interest in clinical research.

Influenza Viruses

IT is now clear that influenza A differs distinctly from influenza B. This difference is reflected clearly in experience in Europe during the past two winters. During the winter of 1950–51 a large epidemic wave of influenza A started in Scandinavia and spread south across the Continent, while another wave, originally from the Southern Hemisphere, spread northwards until it met the Scandinavian wave.[1] This was a sharp outbreak, rapid in onset and spread, which had a high over-all incidence and caused many n this country alone, cases probably num- 4 million and deaths more than 20,000.[2] By t, influenza B has been prevalent this year, ently in the complete absence of influenza A. Th infection has been sporadic, with only small localised outbreaks in Holland, Italy, and Sardinia, and, in Britain, in Glasgow and the south of England. *It is difficult to detect any wave of infection*, and the outbreaks appear to have been independent of one another. In fact, influenza B does not deserve the name "epidemic influenza" in the same way that A does.

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[1] See *Brit. med. J.* April 26, 1952, p. 917.

[1] Isaacs, A., Andrewes, C. H. *Brit. med. J.* 1951, ii, 921.

Influenza affects all ages and imparts relatively brief immunity. A priori, therefore, a virus like influenza A which causes large epidemics every two to three years might be expected to undergo regular slight antigenic modifications in order to maintain its epidemiological reputation. This is, in fact the case; influenza-A viruses isolated from successive epidemics are generally slightly different from those which came before. On this type of reasoning, it might be expected that influenza-B viruses isolated in different years would be much more similar to one another; and that this is so is suggested by a study from the World Influenza Centre in London. Bozzo,[3] has made an antigenic analysis of 30 influenza-B viruses isolated in different countries during the past twelve years. The first influenza-B strains isolated from the 1940–43 period seem to stand by themselves. However, 27 strains of 1944 vintage or later proved reasonably homogeneous when compared by agglutination-inhibition tests. Since the earlier strains were first grown in ferrets and mice and then eggs, while the later strains were isolated and maintained in eggs, the differences might be more apparent than real. Essentially similar conclusions were reached by BRANS[4] in a parallel study made in Prof. J. MULDER's laboratory in Leiden. American work,[5 6] on the other hand, suggests that strains of influenza B isolated in different years differ antigenically; but Bozzo maintains that this conclusion may have resulted from a lack of uniformity in the methods of investigation. One practical suggestion made by both Bozzo and BRANS is that the Lee (1940) strain of influenza B should be replaced in vaccines by a more recent B strain. This seems most reasonable. At the same time many will question the wisdom of ever including influenza-B viruses in vaccines, as long as the influenza-B viruses cause small outbreaks and show no epidemiological ambitions.

The antigenic characters of influenza viruses are discussed from a more theoretical viewpoint by Professor WILSON SMITH in his Sydney Ringer lecture, printed elsewhere in this issue. WILSON SMITH describes the continued emergence of new antigenic subtypes of influenza virus from the first isolated strain in 1933 (with which he himself was closely associated). He renews his plea, however, for less attention to the antigenic characters and closer investigation of other properties, partly on the ground that the virulence of a virus may vary independently of antigenic changes and partly on the practical grounds that virus variation may take place so rapidly that the virus is always one step ahead of any protective vaccines.

It is true that antigenic modification cannot be said alone to affect the virulence of a virus—largely because virulence is influenced not only by the virus but by the susceptibility of the host. A single antigenic type of virus may cause mild influenza in a partly immune population such as our own, and yet devastate a highly susceptible population; the same is true of other virus diseases, such as measles. Many workers would certainly agree with WILSON SMITH that while the antigenic characters of an influenza virus may contribute substantially to its virulence they are not the sole factors. The difficulty then arises—which characters give the virus its bite? Research in WILSON SMITH's department has concentrated on the influenza-virus mucinase, by which the virus attaches itself to susceptible cells. Results of great theoretical interest have been obtained, but it cannot yet be claimed that this enzyme is the teeth of the virus.

Towards the close of his lecture WILSON SMITH gives a speculative hypothesis of the structure of the influenza virus. Some would perhaps accuse him of understatement in saying that ether distorts the surface architecture of the virus: it breaks up the building. There are also other schools of architecture, which would not accept WILSON SMITH's hypothesis that host protein forms a central skeleton round which influenza virus is built up, and would prefer to regard it as outer scaffolding left by careless workmen. But there is no doubt that the combined researches of the theoretical architect and his practical surveyor colleague will in time give us the blueprints of the influenza viruses. Let us hope that between them they will also tell us how to prevent influenza.

Burns Units

DEATH or serious scarring of burned people is nearly always caused by infection—once the hazard of all major surgery. We have chemotherapy to help us nowadays, but this alone will not serve to keep a burn sterile and so fit for early grafting. Dr. LEONARD COLEBROOK, in his years at the Birmingham Burns Unit, showed us that chemotherapy must be used in conjunction with an exacting aseptic technique, which can only be applied if the structure and equipment of the burns centre are specially designed to make this possible. In his book, *A New Approach to the Treatment of Burns and Scalds*,[1] he described a design for such a centre in detail, and his advice and experience have not so far been given the attention they deserve.

The principles are those of operating-theatre technique modified to suit a different problem. All dressings, he says, should be done in air that has been freed completely of dust, and almost completely of micro-organisms; they should be done by a trained team, using strict aseptic technique; chemotherapy, guided by bacteriological findings, is essential; patients should be nursed in cubicles; a bacteriologist should act as infection control officer; an operating-theatre and anæsthetist should always be available, so that grafting can be done at the best possible moment; and one or more centres providing these facilities are needed, COLEBROOK believes, in every large city. On a previous occasion[2] we described the likely course of the illness in a burned patient treated in such a centre; and in one treated in an ordinary general hospital. It suffices to say here that burns can become infected at the initial exposure, and again whenever they are dressed. In the ordinary ward, moreover, they can become infected between dressings, by micro-organisms transported in the air or in dust. It is almost impossible to keep some burns—especially of the lips, nose, buttocks, and perineum—efficiently covered with dressings all the time. Then the patients are usually children, who may be intolerant of itching, or confirmed wrigglers. Again, the dressings may become soaked with serous exudate, and organisms may grow through them from the outside. Yet the successful treatment of burns depends on preventing contamination with pathogens; for a burn that has been kept free of infection can be grafted within a fortnight or three weeks—and indeed some burns can be grafted on the very day of the injury. With an experienced surgeon, some 90% of the grafts take, and healing is complete within six or eight weeks of the accident, usually without contractures. The story of the infected burn is very different. The child is seriously ill for at least three or four weeks, and if she (or less commonly he) survives, it may be many weeks more before the burns are clean enough for grafting. As the granulations are by then tough and fibrous, grafts do not take readily; and if the first one fails so may the rest. Moreover the child may not have much whole skin left; and in the end the healed burns may be so scarred and contracted that she is deformed for life. She has also suffered much severe pain.

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[2] Bradley, W. H. *Proc. R. Soc. Med.* 1951, *44*, 789.
[3] Bozzo, A. *Bull. World Hlth Org.* 1952, 5, 149.
[4] Brans, L. M. Studies on the Antigenic Composition of Influenza Virus B Strains. Leiden, 1952.
[5] Tamm, I., Kilbourne, E. D., Horsfall, F. L. jun. *Proc. Soc. exp. Biol., N.Y.* 1950, *75*, 89.
[6] Hilleman, M. R., Mason, R. P., Buescher, E. L. *Ibid*, p. 829.

[1] London: Fine Technical Publications. 1950. Pp. 174. 12s. 6d.

COLEBROOK classifies burned patients arriving at the casualty department of a hospital as those with slight burns who can be treated as outpatients, those with moderately severe fresh burns, those with moderately severe burns of more than twelve hours' standing, and those with severe fresh burns. The admission room and the casualty department (and all who work in them) are contaminated with pathogenic bacteria, and the patients' stay in these regions is therefore a time of special danger. At Birmingham they are seen, and their burns assessed, *by a senior member of the burns team, within fifteen minutes of their arrival in hospital:* in other words they are recognised as emergency cases. In a properly designed burns unit the four classes of patient can be dealt with in different ways. Those fit for outpatient treatment will be sent to an outpatient dressing-room by way of an airlock. This dressing-room, like other dressing-rooms in the unit, must be air-conditioned; and the airlock serves to prevent the entry of contaminated air into the room itself. Every time an outpatient attends, his burn will be dressed in the clean air of this room. Those with moderately severe fresh burns are sent through a different airlock to the "clean" admission room, and thence into the plenary treatment-room which opens from it. If the burns are suitable for immediate grafting they are cleansed gently and the patient is then taken to the theatre. If they are not, she is taken straight to a cubicle opening on a veranda. A patient with a moderately severe burn received more than twelve hours before admission (and therefore probably infected) goes by way of a third airlock to the "dirty" admission room, thence to the main dressing-station, which opens from it, and thence to a cubicle. The patient with a severe fresh burn is taken at once, through a fourth airlock, to the shock treatment-room. The air-conditioning of these four sets of rooms does not require an elaborate or unduly expensive piece of equipment. At the time when COLEBROOK was writing (1949), a plant to provide 20 turnovers of twice-filtered air per hour in a room of 3000 cu. ft. cost £500. That it kept the air almost free from bacteria was established by experiment. Not only was the bacterial content of the air entering the room remarkably low when compared with that of air samples from other parts of the hospital, but there was no progressive build-up of contamination in the room: the bacterial count rose during the dressing of a contaminated wound, but fifteen minutes after the patient had left the count was back again at the original low level.

The technique of dressing is precise. The wound must be protected against contamination conveyed by means of hands, instruments, towels, cleansing solutions, dressings, or airborne particles; and nothing must be done to the wound that will damage its leucocytes, epithelial cells, fibroblasts, or vascular supply. Dressings must be removed as gently as possible, so as to prevent unnecessary pain for the patient and to conserve growing epithelium. The dressing must be a perfect cover, preventing the entrance of dust particles, and protecting against the ingrowth of pathogens from outside; and the first dressing, if intact, can be left untouched for ten to fourteen days. If the wound remains uninfected, dressing causes little or no pain. These principles can only be carried out by a team trained in no-touch technique and scrupulous to observe details. The plenary treatment at the outset consists in gentle cleansing with a detergent solution, a bland non-toxic application incorporating penicillin, and adequate dressings held in place with plenty of crêpe bandages (which will not stretch and slip), and if necessary encased in plaster.

The preliminary treatment for shock is just as exacting. Within ten minutes of admission a child with severe burns, having been seen by the senior surgeon of the team or his deputy, is wrapped in a large sterile towel and taken to the shock-room. Blood is withdrawn for a hæmatocrit estimation and a plasma drip is set up at once; half an hour after the child enters hospital she has had several ounces of plasma into a vein and is getting frequent sips of fluid by mouth. Other hæmatocrit estimations are made at intervals of two to three hours, to guide the surgeon in regulating the rate of the drip. He visits the patient frequently, and a nurse stays with her all the time to calm her and look after the drip. After four to six hours she is strong enough for the burns to be dressed, and this is done in the shock-room by a team consisting of the surgeon, ward sister, and nurse, all completely covered with sterile clothing and using a strict no-touch technique. At the end of twenty-four to thirty-six hours, if she continues to improve, the child is transferred to a cubicle. For all this care and forethought will be wasted if she is taken, not to a cubicle, but to a general ward. The risks of cross-infection there are too numerous to avoid. Some of them have been mentioned already, but there are others—contaminated feeding utensils or thermometers, toys tossed from bed to bed, contaminated bedpans, infected visitors, and doctors and nurses who on some solitary occasion forget to wash contaminated hands. Cubicles make it easy to avoid most of these dangers because they can be treated as separate units, each with its own utensils and equipment, and because they remind doctors and nurses going into them that the patient has been deliberately isolated.

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[2] *Lancet*, 1950, ii, 175.

This is the heart of the matter: prevention of infection by an elaborate technique, applied in adequate surroundings—the problem which surgery has faced and successfully overcome.

The Intelligent American's Guide to the N.H.S.

As representative of the Rockefeller Foundation in London since 1950, Dr. O. L. PETERSON has had a fine opportunity to observe our medical innovations, and in his *Study of the National Health Service of Great Britain*[1] he offers his fellow-countrymen a reliable guide to the complex structure of interlocking committees, boards, and councils which our national taste for compromise called into being in 1948. A good guide-book is informative before it is discursive: Herr BAEDEKER does not waste time discussing whether it was sensible to build Chartres Cathedral, and, if so, whether it was wise to choose the Gothic style of architecture; and in the same way PETERSON begins by asking his readers to accept, for good or ill, the existence of the N.H.S.:

> "The decision to create a National Health Service was a decision taken by the whole society. It is fruitless to argue whether it was done too rapidly or that too much was attempted in one major change, or whether it might have been better to wait for a more propitious economic situation."

The greater part of his report is thus, of necessity, occupied by his clear and comprehensive account of the scope, administration, and economics of the N.H.S. But he has laced his description with criticism and suggestion, and the judgment of so fair and intelligent a spectator will command the attention of English readers.

The service, he says, is a national service created by the community to meet the needs of the community. Quantitatively, he believes, it has been on the whole a success: "virtually the whole population and nearly all the doctors" have entered it, and in consequence the economic barrier between doctor and patient has been removed and (broadly speaking) everybody in Britain now has a doctor. But of the quality of the care offered he writes less reassuringly. As a simple problem, health should be tackled by a unified administration, and in PETERSON's view the big weakness of the N.H.S. is its division into three branches. In place of this uneasy triformity, he would prefer an all-purpose unit of administration based on the hospital. Under the N.H.S. the hospital services have, he agrees, been strikingly improved, and even by the highest American estimates of need we now have, numerically, nearly enough beds. But he thinks that in their too narrow preoccupation with the care of the sick the hospitals are missing an opportunity.

> "The modern hospital has a much larger part to play in the community than merely providing specialised care for the sick. The hospital has a function as a social institution to aid in the provision of preventive services and in the maintenance of the quality of medical services and the dissemination of health education."

Under the present divided administration, and in the press of their daily duties, hospital authorities do not pause to consider whether some of their clinical work could not with advantage be shifted to the general practitioners, leaving the hospitals free to accept these wider responsibilities.

But if the practitioner is to take over, or regain, some of the work now done in hospital, he ought to be able to do it at least as well as the hospitals are doing it now. And this brings PETERSON to what he regards as the second grave weakness of the service. No doubt, he admits, all was not well with general practice before 1948, but the administrative framework of the N.H.S. has done little to help and something to hinder the practitioner in raising the standard of his work. The capitation fee has intensified competition without offering any extra reward for skill and experience, and the divided administration of the service has further dashed the hopes of many able practitioners by separating them from the hospital and consultant services. Until a new and more discerning method of remuneration has been devised, general practice will continue (PETERSON fears) to have "the last call upon the abler members of the profession." At the same time he recognises that when practitioners grumble about money they are often only projecting a vague dissatisfaction upon a tangible grievance, and that there are other reasons for their dwindling morale. For instance their relations with the local hospital are sometimes uneasy: minor irritations have too often been allowed to grow into active hostility. The hospitals, with honourable exceptions, have been slow to provide general practitioners with pathological and radiological facilities that are freely at the disposal of their own junior staff.

> "The assumption that the mature general practitioner is not capable of exercising the same degree of judgment as a recent graduate from medical school demonstrates how very illogical the results of the administrative separation of the two groups can be."

Again general practitioners feel they have been let down over the promised health centres, and PETERSON is inclined to agree. We have, he suggests, too easily allowed ourselves to be defeated by lack of bricks and mortar. Many of the facilities that were to be offered at the health centres do indeed already exist, and with more rational organisation of our resources we might by this time have had health centres in fact if not in name. The group practices that have grown up leave him dissatisfied, for they do not "mesh the general practitioner services with hospitals and health services."

Any help that we are able to give the general practitioner would pay good dividends, for a higher standard of general practice would have a healthy effect on other parts of the N.H.S. PETERSON sees overmedication, for example, as a symptom of the frustration of doctor as well as of patient, and he suggests that an improvement in general practice might well be the best way of controlling the drug bill. The mental health service, he also holds, must in the future rely more upon the general practitioner.

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[1] Copies are obtainable from Dr. Peterson, London School of Hygiene, Keppel Street, W.C.1.

> "If mental health is ever to become a reality a very quick calculation will show that it would be impossible to plan such services on any other terms than their provision through the general practitioners."

With all these fresh tasks in social, clinical, and preventive medicine awaiting him, we must not forget that the general practitioner has also to cope with a greatly increased volume of his own work. Much of this may be minor illness, but a minor illness is not the same thing as a trivial complaint, and PETERSON'S impression is that there has not really been much abuse of the service by the patient. In short he holds that we have been unwise to treat practitioners with such parsimony; for money invested in providing them with adequate workshops and equipment would probably yield more returns in terms of health than money spent on any other part of the service. It seems likely that the Danckwerts award will give us a chance to right part of this imbalance; and though, when he wrote his report, Dr. PETERSON could not have foreseen this development, at least one of his suggestions shows a prophetic awareness:

> "Greater financial rewards to the general practitioner would be a true economy if this allows him to deal unhurriedly, competently, and effectively with his patients."

So far we have given the general practitioner only the job: now it is time to give him the tools.

Annotations

THE DEHYDRATED INFANT

MUCH of the information concerning the regulation of water and electrolyte balance in man has been obtained in response to the pressing need for guidance in the treatment of dehydration. This need is perhaps greatest in the field of pædiatrics, because young children become dehydrated more rapidly than adults and are prone to gastro-enteritis, which in the past was commonly fatal. Since infants with this disease may continue to have diarrhœa for some days, relief of dehydration and prevention of its recurrence are essential. In many other medical and surgical conditions, too, support of the patient by measures to combat dehydration contribute largely to his chances of recovery. The value of these measures has been enhanced by the wide choice of antibiotics to control infection, so that there are now fewer pathological states in infancy which need be expected to cause death once the patient has survived the acute phase.

In the treatment of dehydration the emphasis has moved away from techniques for administering fluids parenterally. Of first importance is an intelligent grasp of principles to guide the choice and amount of fluids to be given; for otherwise the dangers of treatment may exceed those of the original disorder. Recognition of this need has led the Medical Research Council to sponsor a memorandum on the treatment of acute dehydration in infants.[1] The aim is to help those responsible for the day-to-day care of infants, and therefore the subject is presented in a somewhat simplified form; but references are given to fuller accounts of the dehydration process and to some of the original work on which our present understanding of fluid and electrolyte requirements is based.

Severely dehydrated babies are few compared with the large number with slight dehydration due to transient causes, whose progress to recovery will usually be straightforward. Early recognition will sometimes enable treatment to be undertaken at home if proper supervision is possible. It is clear, however, that infants suffering from the more severe and long-continued disorders are best treated in specially equipped and well-staffed hospital units.

Experience has shown that most of the severely affected infants do well if their dehydration is relieved by parenteral infusion of solutions of sodium without potassium salts, and that administration of potassium can safely be deferred until fluids are tolerated by mouth. In some, however, tolerance to oral feeding is long delayed, and these may become dangerously depleted of potassium. At the outset those likely to make slow progress cannot be distinguished from the rest; and the memorandum recommends that potassium should usually be given to dehydrated infants who have sustained electrolyte losses. Danger from giving potassium in this way can be avoided by two precautions: (1) spacing evenly throughout the twenty-four hours the administration of dilute solutions of electrolytes; and (2) adjusting the total fluid intake to ensure a free flow of urine, which should be checked by examination of samples at 12-hourly intervals. Here the memorandum's advice is at variance with the conclusion reached by Black and Milne.[2] These workers, however, based their opinion on a study of experimental potassium depletion in two normal adults; and thus the conditions were unlike those in clinical dehydration, where it may not be possible to detect the transition from moderate to severe potassium depletion in very sick patients, whose signs of weakness may be wrongly attributed to another cause. Moreover, dehydrated infants usually receive a much larger volume of fluid per unit of body-weight than do adults. Consequently they pass more urine, and the danger of including potassium in fluids for intravenous infusion is thus avoided.

The clinician may perhaps best safeguard his patients by bearing in mind the title of Professor Gamble's[3] latest contribution to our understanding of fluid requirements in dehydration: "The companionship of water and electrolytes in the organisation of the body fluids."

CORTISONE AND CAUTION

IN the excitement which customarily follows the discovery of a new and potent therapeutic weapon, it happens far too often that traditional and tried methods of treatment are neglected. It may be that these older methods were not strikingly effective: in an age which expects cures and to which miracles are commonplace, the fact that most diseases are incurable is forgotten, as well as the important rider that most diseases may be ameliorated by treatment.

New steroids and new moulds each have their place in the framework of treatment, but these do not warrant the jettisoning of established methods. The increasing use of cortisone in rheumatoid arthritis has led to a situation where many physicians who formerly had little interest in the rheumatic diseases are treating cases which would once have been referred to the "rheumatism clinic" or to the physician in charge of the physiotherapy department. The neglect in some instances of fundamental measures of therapeutic care, such as the use of heat, assisted exercises, and splintage, has caused experienced physicians ("B.C. rheumatologists," as Hench put it, as against "A.C. rheumatologists"—after cortisone) to raise a warning voice and to emphasise that it is essential to continue, along with newer forms of treatment, what a group of workers at the Mayo Clinic have called a basic "conservative program, including physical medicine, adequate rest, diet, simple analgesics and other general supportive measures."[1]

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[1] The Treatment of Acute Dehydration in Infants, by a working
dvised by the Committee on Acute
ledical Research Council memorandum
Office. Pp. 49. 3s.

[2] Black, D. A. K., Milne, M. D. *Lancet*, Feb. 2, 1952, p. 244.

[3] Gamble, J. L. Lane Medical Lectures. London, 1951.

The comparison made by this group between 34 patients treated with a basic régime including physical medicine and 54 patients treated with cortisone in addition is of great topical interest, particularly so since it emanates from the Mayo Clinic. They found that 85% of the cortisone group showed objective improvement, as against 80% of those treated similarly but without cortisone—a difference which on testing statistically for significance is found to be negligible. The groups were similar in most respects, but the cortisone group contained a larger proportion of chronic cases (63% with a duration of 5 years or more, compared with 47% in the control group), and it is stated that this type of case shows less improvement with conservative treatment than cases in which symptoms have been present for a lesser time. Even in this type of long-standing disease, however, the difference between the cortisone-treated and control group does not reach significant levels: the observed difference in the numbers improved in the two treatment groups (62% and 85%) gives a value for χ^2 of 2·1 and might occur by chance alone in more than 1 out of 10 therapeutic trials if the treatments were absolutely the same. The use of such statistical checks would improve a lot of the papers appearing on this subject, but many aspects of treatment cannot be put into figures. Those who have had some experience in the use of cortisone in cases of rheumatoid arthritis will agree with the authors' modest statement that "Cortisone is an important adjuvant to the treatment programme of many patients with active rheumatoid arthritis."

TUMOURS OF THE MEDULLA OBLONGATA

INTRINSIC tumours of the medulla are uncommon, but a report from the Mayo Clinic[2] reviews 15 cases in which the tumour was confined to the medulla or in which extension into the pons or spinal cord was minimal. In 14 of these cases the extent of the tumour was verified at necropsy, and in the 15th the site of the tumour was confirmed at operation. Despite the crowding of cranial nerve nuclei and ascending and descending fibre tracts in the small space of the medulla, the clinical picture of these tumours is far from uniform and there may be very few neurological signs. The reason is the relative resistance of axis-cylinders and ganglion cells to pressure from an infiltrating glioma. Pathologically 11 of the tumours were gliomas—7 astrocytomas, 2 glioblastomas, 1 ependymoma, and 1 oligodendroglioma—while the remaining 4 were hæmangio-endotheliomas. The common early symptoms were: ataxia, partly of cerebellar origin and partly due to disturbance of proprioception from involvement of the cuneate and gracile nuclei; headache, chiefly in the occipital region; and weakness of the limbs. This weakness was due to pyramidal tract involvement, but in contrast to gliomas of the pons, where pyramidal involvement is usual, it was present in only 9 of the medullary tumours—probably because the pyramidal fibres are more diffuse and widespread in the pons than in the medulla, where they are grouped on the ventral aspect, and the majority of the tumours occur in the dorsal two-thirds. Cranial nerve dysfunction was found in 7 of the patients, and often more than one nerve was involved; there was facial weakness in all 7 cases and sixth nerve paresis in 6. In some of the patients the sixth nerve was compressed by the enlarged medulla as it passed between the pons and medulla, but the Mayo Clinic workers do not explain the unexpected frequency of facial nerve involvement by tumours apparently confined to the medulla. Of the lower cranial nerves the twelfth was involved in 3 patients, the eleventh in 2, and the ninth and tenth in 4. There was raised intracranial pressure in only 6 of the patients; and hiccup was a prominent feature in 5 cases, in 2 of which this was an early symptom. A surprising feature in 2 cases was epileptic fits, and no definite explanation for this was found.

There is considerable difficulty in the clinical diagnosis of intrinsic tumours of the medulla oblongata, owing to the great variability of the symptoms and physical signs. In these patents there is a real danger of sudden unexpected death from acute respiratory failure.

"SALT-LOSING NEPHRITIS"

IN 1944, Thorn et al.[1] described two cases in which electrolyte disturbances due to advanced chronic renal disease gave rise to a clinical picture akin to that of Addison's disease with crisis. This diagnostic difficulty has since been reported by Sawyer and Solez[2] in a case of nephrocalcinosis, and by Nussbaum et al.[3] in a case of chronic pyelonephritis. In these patients the absence of hypertension or preceding acute renal disease, together with the absent or very slight albuminuria, delayed recognition of the underlying renal disease; and the raised blood-urea and sodium depletion were attributed at first to adrenocortical insufficiency. Subsequently, failure of the blood-urea to fall to normal after the sodium depletion was corrected by adequate salt intake, and such findings as normal glucose tolerance, normal 17-ketosteroid excretion, and normal suppression of eosinophils by A.C.T.H., led to recognition of the renal disease.

In chronic nephritis minor degrees of dehydration are common, and care has to be taken to ensure an adequate sodium intake.

Platt[4] conceives of the failing kidney as one with a reduced number of nephrons working under conditions of osmotic diuresis due to the high blood-urea and therefore failing to conserve sodium. Generally patients with chronic renal disease remain in fair balance for sodium and potassium even with quite a large range of intake of these ions. On the other hand, some of them show a tendency to excessive sodium loss, and Platt describes these as potential cases of "salt-losing nephritis." The overt case of sodium depletion with vasomotor collapse is probably only the extreme example of this failure to conserve sodium. Just as sodium depletion from any cause can bring about renal insufficiency in the absence of organic renal disease, so it can further reduce function in an already diseased kidney. A vicious cycle is then set up; and it is understandable that azotæmia, weight-loss, vomiting, and vasomotor collapse may stimulate an Addisonian crisis. In such cases the tubules may perhaps be more severely damaged than the glomeruli, and the resultin [illegible] imbalance may account for the failure [illegible] This recalls the ion-depletion states [illegible] in the early diuretic phase of acute tubular necrosis.[5] Gross sodium or potassium deficiency may then arise unless enough of these elements is ingested to balance the uncontrolled urinary losses occurring while the tubules are being relined with immature epithelium.

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1. Martin, G. M., Polley, H. F., Anderson, T. P. *J. Amer. med. Ass.* 1952, 148, 525.
2. Cooper, I. S., Kernohan, J. W., Craig, W. McK. *Arch. Neurol.*

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1. Thorn, G. W., Koepf, G. F., Clinton, M. jun. *New Engl. J. Med.* 1944, 231, 76.
2. Sawyer, W. H., Solez, C. *Ibid*, 1949, 240, 210.
3. Nussbaum, H. E., Bernhard, W. G., Mattia, V. D. jun. *Ibid*, 1952, 246, 289.
4. Platt, R. *Lancet*, 1951, i, 1239.
5. Bull, G. M., Joekes, A. M., Lowe, K. G. *Clin. Sci.* 1950, 9, 379.

With sodium depletion of renal origin, treatment consists simply in quantitative replacement of sodium, usually as a mixture of sodium chloride and sodium lactate intravenously, followed by a liberal intake of salt in the diet. In the case reported by Nussbaum et al., despite the presence of polyuria, hyperpotassæmia accompanied the sodium depletion. Adrenocorticotropic and adrenocortical hormones did not appreciably affect the renal losses of sodium; but possibly they protected against the harmful effects of hyperpotassæmia. In Nussbaum's patient sudden unexpected death, probably due to hyperpotassæmia, followed the cessation of cortisone therapy during treatment with sodium acetate to counteract the acidosis of renal failure. Despite the lowering of the plasma-potassium level, death was attributed to potassium poisoning; and Nussbaum cites experimental evidence that alkalinising salts promote death from hyperpotassæmia, whereas adrenal hormones increase tolerance of it.

CONTROL OF RAT POPULATIONS

Rat control, even by the newest methods of poisoning, remains exceedingly difficult and very expensive.[1 2] Davis[3] has suggested that a solution may be found, not in new poisons or baiting methods, but in the study of the behaviour of rat populations. If a few rats begin to breed in a favourable area their rate of increase will be slow at first, then more rapid; but as the area fills up increase will slow down until a maximum number is reached.[3 4] One implication is that reduction of such a population by about half (a common result of attempted control) merely brings it to the level at which it increases most rapidly. When, in Baltimore, half a rat population was caught by trapping, the survivors rapidly gained in weight, and within two months the pregnancy-rate had doubled.

The decline in population growth, and the final equilibrium are due to adverse factors whose effects increase with the density of the population. The more rats there are, the greater will be "predation" by man, dogs, and hawks; the greater will be the pressure on nesting sites; and the less food there will be for each rat. Calhoun[5] has shown that rats which were able to nest near food were more fertile and grew more rapidly than those farther away—evidently because the latter, when on their way to food, were attacked by the others. From facts of this sort Davis concludes that "predation," including poisoning and trapping, is not profitable, and he advocates instead action to "increase competition" among the rats themselves.[3] He claims that, by reducing access to food and clearing away harbourage, the rat population of Baltimore was reduced from about 400,000 in 1944 to about 65,000 in 1949.

Meanwhile, however, methods of direct destruction will continue to be used; and for these, too, knowledge of population changes is needed. An authority with limited resources needs to know the most economical way of applying them. This requires: (*a*) a knowledge of the effects on rat populations of particular methods of control, and (*b*) quantitative information on rat-population levels and the amount of disease or food destruction they cause. During the late war the use of the pre-baiting method, with carefully tested poisons, brought rat infestation of Government food stores to a very low level.[6] On the other hand, little impression seems to have been made on the rat population of rural areas.[4] To investigate food losses, Barnett[7] exposed bagged wheat to small numbers of rats for 12–28 weeks: the total loss was 18% of the original value of the wheat plus sacks, but nearly two-thirds of this loss was due to damage to the sacks. It is sometimes said that rats cause more loss of food by fouling than by eating it; but in these experiments, although 70% of the wheat was fouled, it was all deemed fit for human consumption after cleaning. Barnett[2] concludes that a rational scheme of rat control requires much fuller information, both ecological and economic, than has yet been brought to light.

CONFINEMENT IN HOSPITAL ?

At last week's Margate congress of the Royal Sanitary Institute one of the sections had a useful session on Hospital Midwifery versus Domiciliary Midwifery. The opening speakers were an obstetrician (Mr. Rufus Thomas), a medical officer for maternal and child health (Dr. Elspeth Warwick), a superintendent of midwives (the Hon. Eve Chetwynd), and a general practitioner (Dr. Talbot Rogers), and they agreed that hospital and domiciliary midwifery should be complementary services, and therefore need coördination. The extent of hospital provision varies widely in different areas, and it is rarely planned in concert with the local health authority. However many maternity beds are provided they seem to be generally full, and though the demand for them is often based on social rather than medical needs, it appearss likely to continue so long as shortage of houses obliges so many young couples to begin their married life without proper homes. Both Dr. Warwick and Miss Chetwynd regarded the domiciliary midwife as the best judge of the social *indications* for hospital confinement. Both thought, too, that the Ministry's circular last year on the Selection of Maternity Cases for Admission to Hospital advocated too strongly the admission of primigravidæ and of multigravidæ with more than four children. Mr. Rufus Thomas listed a series of types of medical and obstetric difficulty that should always qualify for admission; and he would also admit all primigravidæ aged over 35 and all elderly multigravidæ.

In 1946 the Royal College of Obstetricians recommended that hospital beds should be provided for 70% of confinements. Lack of money and other resources has made this impracticable, and Dr. Warwick and Miss Chetwynd alike believed that something much less—probably about 50%—is quite enough, so long as the selection of cases is satisfactory. Dr. Rogers argued that the two factors governing the proportion of cases admitted are (1) long-standing local custom, and (2) the number of beds. The demand for beds is high and will remain so. The Ministry's circular has done nothing to increase the number or proportion of domiciliary confinements; nor is there evidence that admission is being granted only to mothers who can show medical or social need. He believed that all the maternity beds provided will always be used; that with a falling birth-rate the proportion of hospital deliveries will rise; that this will mean a higher proportion of uncomplicated cases in hospital; and that many of these cases will not require specialised help. He therefore favoured setting aside, in hospital, beds where women being confined could be cared for by their own doctors and midwives. Mr. Rufus Thomas, though approaching the problem differently, came to not dissimilar conclusions; for he sought to cure underemployment of midwives, and underestablishment and overworking of trained hospital staff, by bringing the midwife into the hospital for part of her time. He would also like to see the G.P.-obstetrician "fitted into the hospital structure in such a way as to bring him into close relationship with the consultant staff."

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1. *Lancet*, 1951, i, 333.
2. Barnett, S. A. *Surgo*, 1952, 18, 111.
3. Davis, D. E. *Amer. J. publ. Hlth*, 1951, 41, 158.
4. Barnett, S. A., Bathard, A. H., Spencer, M. M. *Ann. appl. Biol.* 1951, 38, 444.
5. Calhoun, J. B. *Ann. N.Y. Acad. Sci.* 1950, 51, 1113.
6. Barnett, S. A. *Ann. appl. Biol.* 1947, 34, 297.
7. Barnett, S. A. *J. Hyg., Camb.* 1951, 49, 22.

Dr. Catherine Crane (M.O.H. for York) disagreed with the suggested part-time use of domiciliary midwives in hospital, and suggested that where such a midwife is not fully employed she could more usefully devote some of her spare time to helping general practitioners with antenatal examinations at their surgeries or with the postnatal care and examination of their patients, and to training the mothers in mothercraft. The mothers could with advantage remain under the supervision of the midwife for the whole of the first month of the child's life.

Contributions from the U.S.S.R. (Professor Hohol), the Netherlands (Dr. C. Banning), and Belgium (Dr. van Meirhaeghe) showed that these countries have problems akin to our own, but suggested that the proportion of hospital confinements is still appreciably lower on the Continent than it is here.

SPREAD OF INFECTION IN FAMILIES

THE family has been much in the news as a unit for social studies, but it has been neglected as a unit for the study of the spread of infective diseases. Yet infection often reaches patients through members of their families; and the family is also a small and convenient group for trying to elucidate some of the methods by which infection is spread. Much useful information could be extracted from records kept by general practitioners visiting the home at intervals during an outbreak of illness. Such records might include: (1) the nature and date of onset of symptoms in the first patient; (2) his age, sex, and position in the family; (3) the number of household contacts and their previous experience of the disease under investigation; (4) the dates of onset of any symptoms in the contacts; and (5) the results of periodic bacteriological or virological examination of the patient and contacts.

Such records could be analysed in a number of different ways. Watt and Walton,[1] for instance, comparing the "spreading powers" of shigella and salmonella infections, found, perhaps surprisingly, that salmonellæ were as likely to spread in a family as were shigellæ. By comparing infected with non-infected families of similar constitution and environment, they noted also that *Shigella alkalescens*, whose pathogenic properties have often been in question, behaved like a non-pathogen rather than a pathogen. The information could be used in other ways. We might obtain evidence on physical method of spread from the differences in incidence of secondary cases, if any, when the first victim in the family is an infant or adolescent, or the father or mother. The effect of age on susceptibility to such common infections as measles, mumps, chickenpox, rubella, and whooping-cough should be readily ascertainable from the combined records of many families in which a child has exposed one or more susceptible siblings. In diseases due to bacteria that are readily isolated in the laboratory, there is a wide field for investigation of the proportion of symptomless infections to clinically manifest infections, and assessment of the factors that affect this proportion.

McFarlan[2] has suggested that study of the spread of infections in families might give information on incubation periods; but others are doubtful—in a household where the patient and siblings are in constant contact it is difficult to determine exactly when infection takes place. Francis et al.[3] in the U.S.A. have demonstrated with regard to poliomyelitis that at least two-thirds of family contacts of a case will be found to be excreting virus. By comparing the isolation of virus from family contacts, less intimate contacts, and people in the general community, they have shown that even in epidemics virus is seldom isolated from persons other than family or household contacts; and they have thus weakened the fatalistic concept (so far as control of outbreaks is concerned) that poliomyelitis virus is widespread in a community during an epidemic.

At a meeting of the section of epidemiology and State medicine of the Royal Society of Medicine on April 18, Dr. W. C. Cockburn described the use of the family unit in evaluating active and passive prophylactics. In the Medical Research Council whooping-cough vaccine trials[4] he found a pertussis attack-rate of 80–90% in the unvaccinated control children (aged 6 months to 3 years) exposed to infection by a case in the same family. This figure did not vary significantly in the different areas in which the trials were made, and it did not seem to be influenced by the time of year or the incidence of pertussis in the community. Similar attack-rates were reported in control groups of children by American workers. In the present trials this observation was being used for estimating the value of different vaccines, and he thought that in future trials it might be used exclusively. The information was probably more accurate than that obtained by other methods; and by concentrating the follow-up studies on families with one vaccinated and one or more unvaccinated susceptible children, a better return could be expected for the time and effort spent on the follow-up observations. With γ-globulin for prophylaxis he and Dr. J. C. McDonald were using a somewhat similar means for obtaining information about measles. Practitioners who asked for globulin to protect their patients were asked to report on the severity of the illness in those who were inoculated. About 80% of the forms were being completed; and preliminary analysis had shown that, contrary to expectation there appeared to be little difference in the protection obtained by inoculation 0–4 days, 5–8 days, or more than 9 days after first exposure.

Dr. R. E. O. Williams described some investigations of the natural history of streptococcal infections among children in an orphanage. These children live in groups of about 12, or sometimes more, in separate houses. Even with "families" of this size a case of streptococcal sore throat was followed by secondary cases in only about one-third of instances; but sometimes as many as 84% of the children became ill. Furthermore, on seven occasions when only one or two of the children became ill, the bacteriological attack-rate varied between 10% and 100%. The differences were apparently due partly to differences in the infecting type of streptococcus.

Mr. O. M. Lidwell, D.PHIL., summarised a study of the spread of the common cold in families in an isolated village near Salisbury.[5] The families were visited weekly and were asked whether they had had a cold in the previous week. Adults living in households with no children suffered, on average, about 1 cold per year, those living in households with school-children had about 2·5 colds per year, and the school-children in these households had 3·7 colds per year. Anyhow in country districts, the school-child is the common-cold nigger in the family woodpile; and further studies are in progress to see whether this is also true in urban areas.

The meeting showed that a wealth of research material awaits the investigator who studies the family unit; but it was also clear that the material cannot be extracted without repeatedly visiting the family. Epidemiology of this sort cannot be practised from the desk: an ounce of personal observation and inquiry is worth a pound of punched cards.

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[1] Watt, J., Walton, M. *Amer. J. Hyg.* 1949, 50, 263.

[2] McFarlan, A. M. *Lancet*, 1945, i, 592.

[3] Francis, T. jun., Brown, G. C., Ainslie, J. *J. exp. Med.* 1948, 87, 21.

[4] Medical Research Council *Brit. med. J.* 1951, i, 1163.

[5] Lidwell, O. M., Sommerville, T. *J. Hyg. Camb.* 1951, 49, 365.

Special Articles

DOMICILIARY CONSULTATION IN PSYCHIATRIC PRACTICE

DENIS LEIGH
M.D. Manc., M.R.C.P.

PHYSICIAN, BETHLEM ROYAL AND MAUDSLEY HOSPITALS, LONDON

ONE of the difficulties of psychiatric practice in this country is that the patient is often very reluctant to seek help. Of the many reasons for his reluctance the most important, without doubt, is the fear of certification: for psychiatry is still most often linked with the idea of "the lunatic asylum." Although some advance has been made in dispelling this concept, there is no denying it exists in the minds of both patients and relatives, and alas of doctors too. Practitioners who are sympathetic to psychiatry, and who are impressed by the results of psychiatric treatment, have told me over and over again of the troubles that arise when they suggest to their patients that a visit to a psychiatric clinic would be helpful. The removal of an acutely disturbed patient to an observation ward, either by the use of an urgency order, or by the duly authorised officer, is of course valuable and practical, yet it may not always be in the patient's best interests. How often is such an incident, with its element of compulsion, really necessary?

For the past three years I have made a practice of visiting patients in their own homes before suggesting how they should be treated, and I believe these domiciliary visits may prove an important advance in mental hygiene, which may help to break down old prejudices among patients and doctors alike. The development of a good personal relationship between general practitioner and psychiatrist will be the most useful derivative of the domiciliary visit, and from this will stem the benefits to the patient. For, as Henry Maudsley recognised long ago, the earlier the patient is treated, the better on the whole are the results, and it is the prime responsibility of the general practitioner to recognise early symptoms. He will do this only if he is aware of what these symptoms are, and (more important) of what psychiatry can do for his patients with these symptoms. The teaching of psychiatry has been woefully neglected in the past, and in my experience the domiciliary visit has offered the established practitioner the knowledge he requires.

During 1949, 1950, and 1951, I have made 427 domiciliary visits. As table I shows, 90% of these patients were dealt with by methods which did not involve compulsion. Approximately two-thirds of the group were treated either as outpatients, or as inpatients on a voluntary basis, at the Bethlem-Maudsley combined hospital. The small group referred to an observation ward could have been smaller still if it had been always possible to admit direct to the Bethlem-Maudsley unit: the chief difficulty was the lack of a vacant bed at the time the patient was seen. As about half the group needed speedy admission to hospital, it is essential that the physician who makes the visit has direct access to hospital beds, preferably under his own control. The group who were referred as voluntary patients to a mental hospital were those whose admission could be safely delayed for about a week, and for whom no bed was available in the Bethlem-Maudsley hospitals.

PROBLEMS OF DIAGNOSIS

For the 181 patients visited in 1951 the diagnoses were: depressive reactions 67; neurotic disorders, 39; organic disorders, 24; schizophrenia, 14; senile dementia, 12; alcoholism, 9; acute asthmatic states, 7; hypochondriacal disorders, 6; mental deficiency, 3. There is no reason to believe that this general pattern of diagnosis did not apply in the two earlier years.

The problem the psychiatrist most often has to face on these visits is the risk of suicide. The assessment of this risk usually demands more psychiatric knowledge than the general practitioner possesses, and may be very difficult for the psychiatrist. None of the 451 patients did in fact kill themselves, and in only 2 were suicidal attempts made after the visit. In these 2 patients, described below, I clearly made a faulty assessment of the risk.

Case 1.—Mrs. A., aged 53, was seen on Nov. 29, 1951. She had been depressed since a son was killed in 1944. After visiting his grave in Belgium in 1946 she became worse: she took to her bed, and stayed there 19 months. She was admitted to the Maudsley in June, 1950, but against advice left after 11 days. Contact with her was lost until November, 1951, when I was called to see her. I found her still depressed and lacking in energy. As she refused to enter hospital I agreed to treat her as an outpatient. An energetic attempt was made to get her to take some interest in herself, and she began to improve. However, on Dec. 20 she inflicted a deep gash in her throat which required 18 sutures. Since the suicidal attempt she has improved continuously.

Case 2.—Mr. B., aged 55, was seen on Nov. 16, 1951. A widower, he lived with his only son of 21, and together they carried on a small business. The impending call-up of the son, and an emotional tangle with a widow, led him to make a half-hearted suicidal attempt by throwing himself downstairs. When I examined him he was moderately depressed, but denied any suicidal thoughts. I decided he could be treated as an outpatient and he attended my clinic on Nov. 29. He seemed better and more cheerful. On Dec. 3 he threw himself out of a window, breaking three ribs, and was then admitted to an observation ward. He was later transferred as a voluntary patient to the Maudsley Hospital.

The importance of a sound medical training is noteworthy, for in 13% of this group the diagnosis originally made, and later confirmed either by inpatient study or by follow-up, was of an organic disorder. The psychiatrist is often called in as a last resort—when no firm diagnosis has been reached by the general practitioner or his medical and surgical colleagues. A tentative diagnosis of hypochondriasis has most often been made. The psychiatrist is all too often the butt of his fellow practitioners for his alleged ignorance of general medicine, and when he diagnoses an organic disorder he needs to do so with great tact. Patients with multiple secondary deposits, cerebral syphilis, epilepsy, tabes, myxœdema, acute poliomyelitis, coronary thrombosis, cardiac asthma, tuberculosis meningitis, and pernicious anæmia have all been referred to me on occasion. The following examples are typical:

Case 3.—Mr. C., aged 48, was seen on June 22. On the 17th his favourite daughter had married against his wishes. On the following day he had a severe headache and his speech became slurred. By the next morning his right upper limb was weak, and he "collapsed" and was put to bed on June 21. In view of the emotional disturbance created by the marriage, the doctor had diagnosed hysteria. On examination, however, the patient was found to have slight right-sided pyramidal signs, and a cerebral thrombosis was diagnosed. He was admitted to hospital where a diagnosis of syphilitic vascular disease was made.

Case 4.—Miss D., aged 60, was seen on Aug. 11, 1950, because her doctor had noted a mental change over the previous three months with depression, and generalised aches and pains. She was considered to be depressed and hypochondriacal. When seen she showed a severe memory defect, with right-sided pyramidal signs. Her liver was enlarged, and there was a pleural rub over the left mid-zone. She was tender to percussion in the dorsal region of the spine. Secondary carcinomatosis was diagnosed, and confirmed later at necropsy.

In my experience the practitioner is more likely to respect a psychiatry which is medically oriented, and a psychiatrist who is conversant with current medical problems and advances. What the psychiatrist does with

TABLE I—NUMBER OF PATIENTS VISITED AND TREATMENT RECOMMENDED

Year	1949	1950	1951
No. of visits	93 *	153	181
No. of doctors referring	58	63	79
Disposal to observation ward ..	8(*9%*)	23(*14%*)	12(*6%*)
Disposal to mental hospital as voluntary patient	9(*10%*)	6(*4%*)	10(*6%*)
Admitted Bethlem-Maudsley ..	31(*34%*)	50(*33%*)	60(*33%*)
Treated as outpatient Bethlem-Maudsley	24(*27%*)	44(*29%*)	62(*34%*)
Advice given to G.P. or family ..	18(*20%*)	27(*18%*)	32(*18%*)
Admitted general hospital ..	—	3(*2%*)	5(*3%*)

* 3 of these were repeat visits.

his own patients in his own time is a different matter; but to talk of the ego, or the superego, to most general practitioners is, on the whole, inadvisable. The translation of psychiatric language into terms which medical graduates understand is an outstanding need. Any psychiatrist who has addressed groups of practitioners will understand the serious difficulties of such a task. In a small way, the domiciliary consultation may do something to help break down this formidable barrier.

It is an interesting comment on these visits that schizophrenics, whose clinical picture is so linked in the public mind with mental disorder, accounted for only 14 visits. Only 2 cases of mania have been seen over the three years: both had to be sent to an observation ward, and both later died while certified patients.

TECHNIQUE OF THE VISIT

There is a spice of adventure about these visits, for psychiatric practice often deals with bizarre situations. But I have only once been assaulted—luckily without effect, though later a policeman had his face kicked in by the same patient. In a recent paper on the acute mental case, the author speaks of turning a hose on to the patient, or injecting sedatives, if need be, through the clothes. I have not had to resort to these expedients; nor indeed has it been necessary to ask the police for help except for this one patient.

The technique of the visit is somewhat different from that of a medical or surgical consultation. Most important is that the visit is made by the psychiatrist alone. The general practitioner is consulted first, but the presence of another doctor at the actual visit is mostly a hindrance to this type of work. The relatives and patients often do not talk so freely in the presence of their own doctor, and the air of informality that is often necessary does not flourish in the presence of two professional men. I am often asked by relatives, and sometimes by the doctor, not to mention that I am a psychiatrist. This I resolutely refuse; and I always introduce myself to patients and relatives as a psychiatrist who has come along to help them. Then I ask "would you like me to try to help you?" Occasionally the patient refuses to talk to me, and then I take a history from a responsible relative.

TABLE II—NUMBER OF DOCTORS REFERRING PATIENTS

Year	1949	1950	1951
Total doctors referring	58	63	79
Number of doctors referring :			
1 patient	45	37	49
2–5 patients	11	22	23
5–10 patients	1	2	5
Over 10 patients	1	2	2

Afterwards I explain to the family doctor and the relative what course of action I advise, and the onus of responsibility for this action is usually placed on the relative. The reason for this is that, besides his duty to the patient, the psychiatrist has, in my opinion, an additional responsibility to help the general practitioner to avoid any of the legal complications that can so easily arise with psychiatric patients. An attitude of confidence and a firm command of the situation are essential, particularly in dealing with the relatives.

PRACTITIONER AND PSYCHIATRIST

The value of these domiciliary consultations is perhaps shown in the steady rise in the number of visits made over the three years (table I). It is also reflected in the analysis of the number of patients referred by individual doctors shown in table II.

One of the interesting demographical facts brought out in this survey is that one doctor may refer many patients, and yet a doctor in the same area may never refer a patient to this hospital. One of my practitioner friends complains that he acts as [illegible] for psychiatric patients, and it is [illegible] his area he is the only doctor who refers patients to this hospital. Although, of course, doctors patronise different clinics, it may be possible that many doctors have no sympathy or facility for dealing with the psychiatric patient, and that this explains in large measure for differences in distribution of patients. And yet the largest number of referrals in 1951 was made by one practice of four partners, none of whom had special psychiatric knowledge but all of whom had an abundance of common sense, efficiency, and understanding of human nature. As a result of this successful coöperation I have had letters from patients in the district where this practice lies, saying they have heard of the "good" psychiatry can do, and asking whether it would be possible for me to see them, even though their doctor is not of these four partners. It would be interesting to study more carefully the result of this coöperation between a general practice and a psychiatrist, which has arisen entirely through domiciliary visits.

TABLE III—ANNUAL NUMBER OF PATIENTS REFERRED

Year	1949	1950	1951
Total referrals	93	153	181
Direct referrals	—	129	151

The hospital, too, gains from the domiciliary visit through the closer coöperation between general practitioner and specialist. Since late 1949, practitioners have been able to choose any consultant, and in this hospital most of my referrals have been from the doctors direct, and not through a domiciliary bureau (table III).

From the consultant's point of view, the domiciliary visit is valuable experience. Many have had no experience of general practice, and one of the constant complaints of general practitioners is that the specialist does not understand the problems of the general practitioner. The consultant confined to his hospital often lives in an ivory tower, and there is nothing so salutary as contact with general practice. In my opinion, an essential part of the training of the specialist should be a period spent in general practice.

Then again, it may perhaps be possible to save much time and money if, by the early treatment of the psychiatric patient, the attitude of the patient and public toward psychiatry changes. A third of the patients visited were treated as outpatients with all the economy that implies. However, this possibility can only arise when an efficient outpatient service is available. Over the three years I have attempted to treat as many patients as possible as outpatients, and I have no doubt that this service could be greatly extended. Outpatient psychiatric clinics with adequate staffing and facilities have proved of great value at the teaching hospitals, but it is useless to expect results if there is not a sufficient staff. With a shift toward more outpatient practice, it is all the more important to see the disturbed patient in his or her own home. Nothing is more likely to terrify the average person than the disturbed patient who arrives in the outpatient department struggling, shouting, or behaving in an impulsive way. It may be very valuable for such patients to enter the hospital as voluntary patients, but the outpatient department is not a suitable place for their reception. The home visit will enable the psychiatrist to arrange their admission at an appropriate time to the appropriate hospital.

In a teaching hospital, such as the Bethlem Royal and Maudsley Hospitals, it is sometimes useful for a registrar to accompany the consultant on a visit. Particularly with students from overseas, the visit provides them with an insight into social conditions which would otherwise be denied them; for every type of home, from a palace to a prefab, has been visited. On the whole, however, I have felt that the presence of a second doctor is not welcome to the patient or his family. For teaching hospitals it might be interesting to institute a system similar to that of the "district" of the midwifery hospital.

CONCLUSION

Domiciliary consultations may well be an important advance in the practice of psychiatry. I believe that their number will increase, and that in consequence a more knowledgeable and friendly attitude toward psychiatry will develop among both general practitioners and their patients.

COLOURING OF NON-INJECTABLE FLUIDS IN OPERATING-THEATRES

The Codex Revision Committee of the Pharmaceutical Society of Great Britain was asked by the Ministry of Health to suggest a standard range of colours for non-injectable fluids used for the storage of ampoules and syringes and for sterilisation of the skin. A subcommittee investigated the subject and has now reported. The report says at the outset that the subcommittee do not "necessarily approve either in general or in particular of the colouring of such fluids," and that the question of its desirability was not considered.

The following principles were used as a guide in deciding the best plan:

(1) Colour should not be used for identification.

(2) Dyes already described in the *B.P.* or *B.P.C.* should be used in preference to unstandardised ones.

(3) Any well-established association between a colour and a substance—e.g., blue for mercuric chloride and red for phenol—should be preserved.

(4) Violet colouring should not be used because of the resemblance to methylated spirit.

(5) Solutions of local analgesics for topical use should be effectively differentiated as a group from all other solutions.

(6) The question of colouring solutions for the storage of hypodermic syringes should be restricted to alcohol (70–75% v/v), which has been described as "the only chemical disinfectant that can be in any way recommended for syringe disinfection."[1]

(7) Solutions for the storage of ampoules are too numerous and should be replaced by one standard solution, so coloured that gross contamination of cracked ampoules may readily be detected.

The report then gives detailed recommendations based on these principles. For example, green is suggested for all local analgesics for surface application, yellow for cetrimide, and magenta for methylated spirit.

The subcommittee conclude by saying that the addition of colour to solutions which are naturally colourless may lead to errors if those handling them attempt to identify them by colour alone. Whenever possible, containers should be labelled.

HEALTH CONGRESS

Medical Presidential Addresses

The annual congress of the Royal Sanitary Institute was held at Margate on April 22–25, under the presidency of Lord Moran, the first doctor to hold this position since 1890.

In his inaugural address Lord Moran remarked that in the last few years the specialists had changed from a highly competitive group—to join which was to take on a gamble—into members of a service; and they were content with the conditions under which they now worked. Furthermore, the general practitioners' grievances were being removed; and the public had got it into their heads that this should be done.

What of the medical officer of health? In some directions the field of public health had contracted. In 1876, when the Royal Sanitary Institute was formed, some of the founders had themselves handled outbreaks of cholera in this country. Now, however, infectious diseases were "a dying industry," and the opportunities in environmental hygiene were not what they once had been. Furthermore, in nutrition, in industrial medicine, in geriatrics, and in psychiatry, the specialist was encroaching on the field of public health.

The job of the medical officer of health was what he made of it; and if the service attracted able men it would be entrusted by the public and the profession with useful and interesting work. (Lord Moran asked whether public health was getting its fair share of men of promise. Did deans advise some of their more able students to go into this branch of medicine?) One task that might lie before the M.O.H. was that of evolving new ways of helping the public. The methods of the public-opinion poll might perhaps usefully be applied to health matters. For example, a quarter of all children under five years of age were not immunised against diphtheria; and if, by inquiry at their houses, it could be found why these children's parents refused immunisation, this would be a long step towards persuading them to fall into line. It was necessary to find new methods of interesting and educating the public; and to know what they were thinking would make this task easier.

Turning to the cost of the service, Lord Moran observed that, with continued expansion without compensatory retraction at any point, the price to the nation could soon be doubled. "If we appeal for any increase in expenditure, we must be able to prove that it is for the public good." The Danckwerts award, for instance, if it were used to encourage doctors to reduce their lists of patients, would be a good investment. Nevertheless, "we must be careful that in seeing that the general practitioner is properly remunerated a balance is kept with the rewards of specialisation." Finally, the profit motive would be nothing like as potent in the next twenty-five years as it had been in the past; and the profession would be wise to concentrate on securing attractive conditions in which to do good work.

THE PUBLIC AND THE SERVICE

Dr. Andrew Topping, president of the section of preventive medicine, remarked that as a result of advertisements of proprietary medicines many patients express a definite preference for such products; and though they may be persuaded to accept something "just as good," much of the psychological value is obviously lost. There is, however, another reason why doctors, often against their better judgment, have to go on ordering bottles of medicines or other types of medicament. "... under the present stresses of a busy practice, the doctor has not time to discuss probable causes or to give advice about sensible living, and he has no alternative, if he is to get through the crowds waiting to consult him, but to put on an air of omniscience, give a snap diagnosis—the more high-sounding the better—and scribble a prescription.

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[1] Medical Research Council war memorandum no. 15. H.M. Stationery Office, 1945.

"There are two grave objections to existing practice. The first is that the British people seem to be becoming a race of hypochondriacs with a considerable admixture of frank malingerers, and I do not see how this regrettable development is to be checked if doctors either choose, or are forced, to play to the gallery in this way. The profession's insistence on 'free choice' of doctor as being one of the essentials has got a lot to do with this problem. There is frequently no real choice whatever, and it does not exist when the patient is really ill and has to be sent for a second opinion or to hospital. Where it does exist, it actually may be the cause of one of the chief defects in general practice, unscrupulous patients making no secret of the fact that they will transfer to another doctor if they are not given a certificate, put off work, or given the variety of medicine they themselves consider advisable. That there are comparatively few transfers shows how very rarely the practitioners refuse: compliance is the easiest way out, and consciences soon get hardened.

"The second objection is that, as a bankrupt nation, we simply cannot go on pouring money 'down the drain' unnecessarily.... It would be a godsend if the family doctors could, or would, take a stronger line with their patients, and assist by stressing the faults of their mode of living instead of placating them with 'bottles.'"

Dr. Topping went on to point out that increasing numbers are admitted to hospital, and the demand is for more and more beds. "The maintenance costs in hospital," he declared, "are getting completely out of hand, and not all the reasons for this are beyond control." After calling for greater attention to preventive medicine and rapprochement between the three divisions of the service, Dr. Topping concluded:

"It is probable that the Ministry of Health is too remote in more senses than one to permit of its being efficient in the control, both general and detailed, which it at present exercises over the preventive and curative services.... I have a feeling that if we could get a new set-up whereby we had units of approximately five hundred thousand—and this would be readily possible in the large industrial areas—and could establish an all-purpose health, welfare, and education authority, many of our present difficulties would disappear. ... Finally, when is Parliament, the public, and the profession going to awake to the fact that health and disease are far too important matters to be left to market-place huckstering? I am convinced that we will have a salaried medical service in ten years' time. Why not now?"

MATERNITY SERVICE

Mr. Arnold Walker, who presided over the section of maternal and child health, was concerned, like Dr. Topping, with the lack of integration. "The unfortunate maternity service was the concern of all three branches, and on July 5, 1948, we saw much of the good work done by the local authorities split assunder, with nothing to hold the three elements together except good will and common sense until the apex of the pyramid is reached at the Ministry."

Mr. Walker went on to say that institutional beds should be provided for those who need them and not those who want them.

"The decision as to the need for a bed on social grounds should rest with the local health authority and not with the institution. The institution should only book direct on medical grounds. To reduce the financial advantage of securing a place in hospital, home helps should be provided on a more generous basis, and some difference made in the benefit received by the domiciliary case compared with the institutional case.... For the normal case, a midwife only should be provided to conduct the labour. If the patient prefers a doctor, she should be able to enter into a private contract with any doctor and have the midwife acting as a maternity nurse. Medical aid should be provided by doctors who have had proper postgraduate training.... Every effort should be made to integrate these doctors into the staffs of local maternity institutions and also to bring them into the clinics as antenatal officers."

THE PUBLIC-HEALTH SERVICE

Dr. W. G. Clark, presiding over the conference of medical officers of health, also considered the working of the three arms of the service. These, he said, are supposed in theory to function as an integrated whole. "We know they do not. They have been fragmented into three parts with the hope that by good will they will work as one. Trial and error and correction will ultimately evolve a really coördinated comprehensive health service, but it will take a long time." Dr. Clark is convinced that the future of public health will be even brighter than has been its past, despite the unevenness of the present distribution of expenditure in the proportions of about 60% on hospital services, 30% on domiciliary curative services, and 6% on prevention. "From their very training the medical officers of health and the public-health staff must become the axis around which all the medical, social, and welfare services will revolve. This conception visualises the local health authorities as the directing forces in a real national health service."

INDUSTRIAL HEALTH SERVICE

Dr. L. G. Norman, president of the section of hygiene in industry, laid down four principles. Firstly, an industrial health service is of the greatest advantage to employers and employees alike. Secondly, such a service should be made available as soon as possible to all industries; and it should be extended to cover non-industrial employment. Thirdly, industrial medicine should not provide treatment except in emergencies. Fourthly, the very large number of small factories without a medical service will need to be included in any plan for future development.

SERVICES IN RURAL AFRICA

Dr. E. D. Pridie, in his presidential address to the section of tropical hygiene, discussed agricultural development and welfare schemes in rural Africa. He urged that special attention be paid to the end-results when planning welfare schemes for the improvement of the medical, health, and social services; for otherwise more problems might be created than were solved.

"Care must be taken not to create hospital and other social services of too high a standard. Otherwise you may be left with white elephants in the way of fine institutions with elaborate equipment or magnificent health services of too high a standard for the local authorities to maintain efficiently when they have to depend on their own financial and human resources to do so."

For rural populations, one solution is the rural health centre, where both curative and preventive medicine are practised. This combination is useful since it is through the popularity of curative medicine that unsophisticated people can be persuaded to carry out the more important, but less popular, measures required to prevent disease. One of the most important functions of rural health centres is to form a network of medical intelligence centres covering the whole rural area of a territory, so that outbreaks of epidemic disease can be reported at once.

REGIONAL HOSPITAL BOARDS

THE Minister of Health has made the following appointments to fill vacancies caused by the retirement of a third of the members of the 14 boards in England and Wales. Out of 130 appointments, 85 are reappointments of retiring members; 8 appointments are still outstanding. Those now appointed will hold office until March 31, 1955. The names of medical members are shown in bold type.

NEWCASTLE REGION

Reappointed: E. F. Collingwood, C.B.E., J.P.; Alfred Cooper; **D. C. Dickson,** F.R.C.S.E.; J. Finegan; John Foster, J.P.; **William Fraser,** M.B.; Robert Muckle; Rev. R. E. Robson.

New Members: A. Charlton Curry, D.C.L., J.P., F.R.S.A.; W. P. McAnany, J.P.; Edward Crowther, C.B.E., Arthur Kay, and **S. Whately Davidson,** F.R.C.P. (till March 31, 1953); **R. S. Venters,** F.R.C.S.I. (till March 31, 1954).

LEEDS REGION

Reappointed: Alderman H. J. Bambridge (chairman); Lawrence Crowther, O.B.E., J.P.; A. F. George, J.P.; **P. J. Moir,** F.R.C.S.; **D. C. Muir,** F.R.C.P.; Miss A. Whalley.

New Members: Alderman H. Bollend; F. Watkinson (Dewsbury) (till March 31, 1953); two appointments outstanding.

SHEFFIELD REGION

Reappointed: Alderman C. F. Bowmer, J.P.; Alderman A. W. Harrison; **J. G. McCrie,** O.B.E., F.R.C.P.E.; Lord Quibell, J.P.; Miss Anne Wetherell, S.R.N.; John Roberts.

New Members: H. S. Essenhigh; Herbert Sands, F.C.A., J.P.; **Gervas Wells-Cole,** B.CHIR., J.P.; one appointment outstanding.

EAST ANGLIAN REGION

Reappointed: Mrs. H. A. Adrian, J.P.; P. F. Dennard; **J. V. Morris,** M.B.; Colonel D. Portway; Miss J. G. Thompson, S.R.N.; Alderman Mrs. M. Whitmore.

New member: **A. J. R. F. Johnson,** M.R.C.S.; one appointment outstanding.

NORTH-EAST METROPOLITAN REGION

Reappointed: Captain H. Brierley, O.B.E., M.C.; **Somerville Hastings,** F.R.C.S., M.P.; Miss D. G. Rootham, S.R.N.; C. S. B. Wentworth-Stanley; C. C. Carus-Wilson, M.C.; A. R. Wood, C.B.E.

New members: S. G. Rowlandson, M.B.E. J.P.; K. E. B. Glenny.

NORTH-WEST METROPOLITAN REGION

Reappointed: Alderman Mrs. B. A. Beaumont, J.P.; Mrs. A. S. Blofield; Sir **Harold Boldero,** F.R.C.P.; M. Hackett; **Horace Joules,** F.R.C.P.; **A. C. Morson,** O.B.E., F.R.C.S.

New members: **J. B. S. Lewis,** M.D.; Prof. Richard Titmuss; J. M. Oakey, M.C., J.P., and **D. F. Hutchinson,** O.B.E., M.R.C.S. (till March 31, 1953); one appointment outstanding.

SOUTH-EAST METROPOLITAN REGION

Reappointed: Alderman R. H. Burslem, J.P.; Dame **Barrie Lambert,** D.B.E., M.B., J.P.; Alderman Rev. Harcourt Samuel; T. S. Stigger; **J. R. H. Turton,** F.R.C.S.

New members: Hon. Mrs. S. L. Henley; Sir **Arnold Stott,** K.B.E. F.R.C.P.; Sir Frederick Wells, BT.; one appointment outstanding.

SOUTH-WEST METROPOLITAN REGION

Reappointed: D. A. J. Jackman, M.B.E., J.P.; **P. H. Mitchiner,** C.B., C.B.E., F.R.C.S.; W. H. Tooes; J. A. Tulk, J.P.; **J. M. Wyatt,** F.R.C.S., F.R.C.O.G.

New members: Lady Brain; Major-General L. A. Hawes, C.B.E., D.S.O., M.C.; Sir Sidney Littlewood; S. L. Collier (till March 31, 1954).

OXFORD REGION

Reappointed: **F. A. Bevan,** M.B.; Mrs. Lilian Davies; Prof. **A. D. Gardner,** D.M.; P. C. Raffety; **J. S. I. Skottowe,** M.D.

New members: Sir Frederick Puckle, K.C.I.E., C.S.I.; Mrs. D. J. Walley; D. W. Lansdown; **W. C. Gledhill,** M.B.E, F.R.C.S. (till March 31, 1954).

SOUTH WESTERN REGION

Reappointed: **N. L. Capener,** F.R.C.S.; Captain F. G. Glossop, R.N. retd; Councillor F. A. C. Riddick.

New members: **C. G. M. Donaldson,** M.B.; Miss I. M. Hodges, S.R.N., S.C.M.; F. Lister, J.P.; **F. C. Logan,** M.B.; **C. S. C. Prance,** M.B., J.P.; Mrs. Charles Williams; one appointment outstanding.

WELSH REGION

Reappointed: Eugene Cross; **H. Graham Davies,** M.R.C.S.; Richard Davies; Mrs. Helena Evans, J.P.; Richard Gronow, J.P.; Rev. B. Waldo Lewis; Prof. E. A. Owen, D.SC.; **D. E. Parry-Pritchard,** M.D.

New members: Miss W. M. Chune, S.R.N., S.C.M.; **Ivor Lewis,** M.D., M.S.; D. Rees Morgan.

BIRMINGHAM REGION

Reappointed: Mrs. Annie Longson Barker; **Norman Duggan,** F.R.C.S.; G. V. Grimshaw; **J. C. Heather,** M.D.; Major Cyril Hotchkiss, J.P.; Prof. **H. F. Humphreys,** O.B.E., M.C., M.B., M.D.S.; Prof. **T. McKeown,** M.D.; **J. J. O'Reilly,** M.B.; Councillor J. G. Parker.

New member: Lady Lettice Cotterell.

MANCHESTER REGION

Reappointed: **Walter Briggs,** M.B., J.P.; Councillor T. Hourigan; Alderman G. T. Marron, J.P.; Prof. **W. I. C. Morris,** F.R.C.O.G.; A. C. C. Robertson, J.P.; R. E. Thomas, J.P.

New members: Miss E. M. Hillier, S.R.N., S.C.M.; L. W. Gibson; Alderman R. Lewis, J.P.; one appointment outstanding.

LIVERPOOL REGION

Reappointed: **D. Brown,** M.B., J.P.; W. Gibbs, J.P.; J. F. Mountford, D.LITT., LL.D.; Alderman **D. R. Owen,** F.R.C.S.E., J.P.; Alma Parkin, J.P.; Prof. **H. H. Stones,** M.D., M.D.S.

New members: Councillor J. Selwyn Jones, J.P.; Miss Frances Peck; Miss G. Riding, O.B.E.

Reconstruction

MARRIAGE AND DIVORCE

Two Programmes of Reform

ONLY the partners in a marriage know what it is really like. A couple who resemble, to the bystanders, Strindberg's Captain and his spouse may consider themselves to be rubbing along very comfortably, while a seeming Philemon and Baucis may not have had a thought or taste in common for thirty years. Compatibility of temperament is not a factor anyone can predict in advance of marriage, especially when bemused by desire. But the ability to make a marriage work turns, perhaps, less on compatibility than on a talent for enjoying half a loaf, and a good grasp of the principle that personal happiness is not a right but a bit of luck.

Both the council of the British Medical Association[1] and the National Association for Mental Health[2] have recently published the memoranda they submitted to the Royal Commission on Marriage and Divorce. These overlap to some extent but the emphasis in them, as might be expected, is somewhat differently placed. The N.A.M.H. see the breakdown of marriage as a failure to maintain a healthy, responsible, and mature human relationship. The criterion of the need for divorce, they say, should lie in the irremediable and complete, or nearly complete, destruction of the marriage relationship. They evidently think that both parties ought to work hard to keep a marriage going. The B.M.A. seem to take a less strenuous view of this obligation, merely recommending that the divorce court "should aim at the relief of suffering and hardship affecting both partners and children, rather than the allocation of blame for the breach of the marriage contract." Both bodies favour the appointment of conciliators, to act at every stage where reconciliation is still possible.

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[1] *Brit. med. J.* April 19, supplement, p. 188.

[2] Memorandum for submission to the Royal Commission on Marriage and Divorce. Obtainable from the National Association for Mental Health, 39, Queen Anne Street, London, W.1.

Under the present divorce law, with the single exception of the insanity issue, a decree is granted where one party can be shown to have consciously violated the marriage contract. The N.A.M.H. do not believe this should be the overriding criterion: "Only an assessment of the total relationship between the partners," they say, "can distinguish between casual acts which may disturb a mainly stable relationship, acts which are the breaking points of a relationship which is no longer tenable, and the persistent attitudes, behaviour, and mutual feeling of the partners which constitute the real basis of marital tension." An isolated act of adultery, perhaps undertaken rashly and impulsively, is often picked on by the injured party as a ground for breaking up a marriage. Yet both the act and the revenge may be symptoms of an underlying disharmony, and if this is tackled there may well be a reconciliation. The offender's remorse, often deep, can be used constructively in such a reconciliation, provided delay is possible and conciliators are at hand. The N.A.M.H. suggest that divorce for adultery should be confined to cases where there have been proved repeated acts, that delay should always be imposed, and that before a decree is given the best possible advice should be taken on the motives at work in the partners. Such advice might be sought, they think, from ministers of the Church, competent social workers, and doctors.

Both the B.M.A. and the N.A.M.H. recognise more kinds of cruelty in marriage than the law does. The N.A.M.H. mention continual hostility, nagging, and disparagement; obnoxious sexual practices in the home; and persistent morose refusal to communicate or converse, to aid and coöperate, to comfort and give affection, or to grant reasonable conjugal rights. They also include acts committed outside the marriage which may injure the partner, the children, or the marriage—such as a sexual perversion carried on outside the home, alcoholism, persistent adultery, irresponsible and concealed extravagance, defamation of the partner's reputation to outsiders, and the like. Yet if all these types of cruelty were recognised as grounds for divorce the marriage tie would surely be much weakened; for a partner who became at all restive would have to hand a wide selection of allegations against the mate, some of which it might be easier to assert than to refute. A solitary day of justified sulkiness could well be magnified into morose refusal to communicate or converse, and a family row into persistent nagging. Only the partners would know what had really been going on. The B.M.A. accept the legal definition of cruelty as "conduct of such a character as to have caused danger to life, limb or health (bodily or mental), or as to give rise to a reasonable apprehension of such danger," but suggest that the conduct should be further described as "wilful or otherwise." For, they say, if the petitioner's health has suffered, it should not be a sufficient defence that the respondent was irresponsible because of drunkenness or insanity. It is perhaps worth pointing out that this introduces a semantic difficulty. "Conduct, wilful or otherwise" leading to these unfortunate results no longer comes under the heading of cruelty, which is by definition (*New English Dictionary*) "a disposition to inflict suffering; delight in or indifference to another's pain." Perhaps this section of the law needs not only redefining or redrafting, but renaming.

The N.A.M.H. point out that, in cases of desertion, the existing law stands in the way of reconciliation; for both partners know that if an attempt at reconciliation fails a further three years of separation will be required before a divorce can be granted. An aggregate of three years, it is suggested, should be sufficient.

Both bodies are concerned for the position of the children after a divorce. All now agree that disharmony between parents or a broken home causes great harm and suffering to children. The B.M.A. recommend that the court should appoint some suitable guardian to the children, and adviser to their parents, until they have reached the age of 16 or even 18. The N.A.M.H. favour the appointment of court welfare officers, to attempt reconciliation of the parents, to guard the children's interests, which they would also represent in court, and later to act as guardians. They also propose that the custody of children should not be assigned according to the technical innocence of the partner selected, but on the basis of what is best for the children's emotional and material happiness. Both bodies agree that marriage between parents should always confer on a child born before the marriage the status of legitimacy, whether or not at the time of the birth either party was free to marry.

The B.M.A. propose that all persons of unsound mind, even if not certified, should be incapable of contracting a valid marriage. The test, they say, should depend on the person's capacity at the time to understand the nature of the contract and the duties and responsibilities created, and on freedom from insane delusions on the subject. They also suggest that mental deficiency should be a ground for nullity whether or not the defective partner had ever been certified or "ascertained" as mentally defective. The N.A.M.H. do not raise this point; but they do not recommend any change in the law to allow divorce of one partner on the ground of mental defect, unless (as at present provided under the nullity clause) defect was not revealed at the date of marriage. A defective parent does not necessarily produce defective children (though it is true that the children are often not very bright); and some defectives prove to be adequate and tender parents. The N.A.M.H. suggest that mental defect should only be a ground for divorce when it leads to behaviour so disastrous as to make preservation of the marriage tie impossible.

Both bodies, while recognising that many socially desirable results have been brought about by the clauses introduced into the law in 1937 (the Herbert Act), note that modern treatment and management of the mentally sick is making it increasingly difficult for doctors to certify that any patient is of incurably unsound mind; and that it is increasingly rare for a patient to be detained uninterruptedly in a mental hospital for as long as five years. The N.A.M.H. would like to see the social behaviour of the partner, rather than the disability from which he suffers, taken as the criterion for granting divorce. The B.M.A. suggest that the criteria should be the actual duration of the disorder as shown by medical evidence, the unlikelihood of recovery, and one year's continuous residence of the patient in mental hospitals or licensed houses immediately before the petition was presented. It is interesting that, in this matter, the concern of the B.M.A. appears to centre in the normal partner, while the N.A.M.H. is more concerned with the sick one. Mental illness is only a form of illness: it is not something apart. It may occur in people who are otherwise good and pleasant mates, and they may recover from it, permanently or transiently, fully or in part. Unless their behaviour makes the marriage impossible, it seems hard that they should be in danger of being cast off for their sickness. No other disease is so penalised; though epilepsy (as well as recurrent fits of insanity) is mentioned as grounds for a petition for nullity in the Matrimonial Causes Act of 1950. The B.M.A. make a strong plea, however, that epilepsy should not be singled out in this way. Surely mental illness deserves to be regarded, nowadays, with similar liberality?

In England Now

A Running Commentary by Peripatetic Correspondents

WE have a steriliser in the passage outside our lab. to deal with the animal-house cages. In pre-Danckwerts days it was a large cubical galvanised box in which steam was generated by the judicious insertion of electrons and water, and a child could see how it worked. Indeed, after a few hours of operation other senses than sight came into play, and most of us could nominate the species from which the contents had been derived. Meanwhile steam leaked gently from every available point, and the temperature of the whole building rose steadily to heat-exhaustion level. To adapt a legal phrase, not only was sterilisation done, it also manifestly appeared to be done.

We have, however, changed all that. The new steriliser arrived the other day and is now finally installed. It is an imposing cylindrical structure, crouched in a corner in a veil of gaily painted pipes. There are dials to tell us when it is about to explode, and by opening some of the fourteen taps and closing others it is possible to bundle parcels of steam from point to point in the interior. There are oil-immersion switches, mercury contact-breakers, rheostats, and a clock by which we all set our watches. Now then, we said, no more sodden notebooks, no more rusty typewriters.

Alas, we have but exchanged our whips for scorpions. In the bowels of the machine there is what we understand to be a solenoid which opens and shuts something with a reverberating and irregular clang of such penetrative power that it has already caused cups of tea to be spilled in adjacent departments and a visiting R.A.F. *type to* become airborne. Plaster is falling steadily throughout the building, and ominous cracks have appeared in the outside wall. Moreover, while the effects of opening certain taps are on balance beneficial, opening others causes vast quantities of superheated steam from the 20th century to disappear into a plumbing system inadequate for the demands of the 19th, with an unearthly rushing sound. Windows rattle, test-tubes tilt and shatter, and learned conversation breaks up into a string of oaths.

For our part, the animals can take their chance: what we always say is, soap and water were good enough for us.

* * *

I have been working with that enthralling but tantalising publication, the Registrar-General's *Classification of Occupations*, which tells us every occupation followed in Great Britain and its social class. In 1950 there were something like 36,000 separate occupations, many of them with names which delight the ear but leave one no wiser regarding their nature. What, for instance, is a Trolloper, a Whammeller, a Nidger, a Jumbler, or a Woffler? What are the precise functions of a Coussie Runner, a Dook Footer, or a Scotchman? What is the daily work of a Buttocker, an Impregnator, a Pipe Doctor, or a Motion Minder? Can Fossil Sorters and Colorado Beetle Operators, Snow Removers, and Cone Collectors really be occupied full time? How does one tell a Flat Walker from a Walk Flatter? Is a Betty Dod Mangler a rival of a Tommy Dodd Mangler? Which is the healthiest occupation, a Masticator (Heavy Chemicals), a Final Viewer of Bullets, or a Night Smoker? Would a Crow Picker or a Table Splitter be a nice man to know? How about the legality of working as a Skull Breaker, an Underhand Busheller, a Swinger, a Slosher, a Lyncher, or a Highwayman? We need not inquire further about, Mediæval Furniture Makers. Is the average Joy Loader as happy as Nature intended? Perhaps only when he forgathers at the local with the Bogie Man and the Pom Pom Man. Suppose my favourite godson wants to be a Spitter: should I encourage him, to give us some influence in the food trade? Or will he spit in my eye when he grows up for not urging the counter-attractions of the life of a Creeper Lad, an Idle Back Maker, a Sagger Wad Pugman, or a Fish Eater Bolster Stamper?

It is all very difficult. True, I have learnt that a Drawing Mistress is employed in the manufacture of canvas, that a Last Remover is not an undertaker but something in the leather trade; and that a Stump Extractor is not what you think at all. But I wish the Registrar-General would put us still further in his debt by producing a *Dictionary of Occupations*. Then I could find out whether a Bar Reeler will be the best part-time job for me when I retire.

* * *

Last week's paper from Birmingham on cœliac disease (p. 836) must have brought tears to the eyes, lumps in the throat, and other signs of deep emotion to many of us who have been house-physicians in children's hospitals or departments. Think of it! All those bits of blotting-paper, on which we calculated calorie values or fat-contents, were spoilt in vain—not to mention the hours wasted from our own young days. While we worked out the changes for tomorrow—the extra $^1/_2$ oz. of potato, the $^1/_4$ oz. less of tomato purée, or the further whack of some vitamin or other—we had only to knock off the poor little blighters' bread, toast, and anything else made of wheat (or rye) flour, and—*Hey presto!*—they would have got well. It's too much. For six months I knew the weight, composition, and calorie value of every item of Boffin's diet, and recited the totals to my chief on his rounds; while poor Boffin himself, on being asked whether he wanted more dinner, would answer "Another $^1/_4$ oz. of rice pudding please." I remember him as a precociously intelligent little chap who looked about 4 but was nearer 9, with a waxy transparent dead-white complexion, a great balloon-like tummy, and spindly legs. But even in those days we had our triumphs. He got well enough to be discharged; relapsed and was with difficulty rescued from another hospital which had admitted him as T.B. peritonitis: but finally went home on his own feet, and even joined up as a motor-cycle despatch-rider in the late war, though I doubt if he ever carried a despatch.

* * *

Calling the other day on a preclinical colleague I found his door forbiddingly closed with a notice saying "This department is closed from Friday, April 11, until Monday, April 21. Please leave salamanders round the back." Being unable to comply with this injunction—I never carry them—I walked sadly away, but it struck me that a technique of this sort might have a wider application, perhaps to my own more pathological activities. I have made out a little notice for my own door. It reads "No stools today, thank you."

* * *

"You can't get very far in medicine without statistics," my scientific colleague told me: and I have never ceased to be grateful for the advice. As a subject for my thesis I had chosen indigestion in infants and was making little progress despite long and painstaking clinical observation. Then my colleague's remark came back to me, and my well-known "Statistical Analysis of Burping in Infants" was the result. A brief summary will show how a simple statistical approach enlivens the dullest subject.

. . . An analysis has been made of the age, sex, weight, and abdominal circumference of the infants and their mothers, together with the effects of breast-feeding, bottle-feeding, father's occupation, age of siblings, and economic status of the family. Assuming a random occurrence of burps one can use the Poisson distribution to describe the probability, p, of 1, 2, 3, . . . n burps, thus:

$$p = e^{-m}\left(1 + m + \frac{m^2}{2!} + \frac{m^3}{3!} \cdots + \frac{m^n}{n!}\right)$$

Our experimental investigation covered a period of 18 burp-hours made by 12 independent observers (11 degrees of freedom). The burp-multiplicity (m) = 0·283 per burp-hour. "Student" t test gave $t = 7{\cdot}138$, which, for 112 degrees of freedom (there were 113 burps per observer), gives a chi-square of 3·8. Analysis of variance showed that the variation within observers gave a mean variance of ± 14·6, which, for 11 degrees of freedom, can safely be neglected. The variance within burps is ±5·3 for 112 degrees of freedom. The correlation coefficient, $r = 0{\cdot}789$.

My statistical colleague tells me that these results are highly significant—of what, I wonder.

Letters to the Editor

TREATMENT OF SCARLET FEVER

SIR,—The correspondence on this subject, despite many dogmatic statements, has not been very helpful to the general practitioner.

The first problem is whether all cases, including the large number of mild uncomplicated ones, should be treated by a series of penicillin injections. Clinically, it would seem that in the mild uncomplicated case, especially in a young child, the cure might be more trying than the disease. Regard must also be had for the possible interference with the treatment of complications or any later penicillin therapy by the production of penicillin-resistant streptococci or penicillin sensitivity in the patient, as occasionally does occur. Paradoxically, Dr. Glaisher (April 19), who in one part of his letter is most unequivocally in favour of treating all cases with penicillin, later appears to contend that the seriousness of the disease is overrated.

Again, the practitioner will want to know how much benefit he can hope to get from penicillin treatment. Dr. Jersild [1] is cited by Dr. Krarup (March 29) as finding an average febrile period of 4–5 days in his penicillin-treated cases. The average febrile period is certainly less at present when penicillin is not used. Dr. Krarup states that, with penicillin, complications completely disappear. On the other hand, Dr. Harries (April 12) cites Dr. H. McLorinan as stating, in regard to his penicillin-treated cases, that " the incidence of complications both before and after discharge from hospital has remained at a low rate." Few hospitals would risk the discredit of an appreciable number of complications after discharge. My experience is that penicillin-treated cases may get further complications, of which I believe only a minority are due to ward infections.

I fail to appreciate Dr. Glaisher's objection to the term " scarlet fever." It has long been known to denote a certain type of toxæmia due to hæmolytic streptococci. That the streptococci capable of producing it can be classified into different types does not alter the position, nor does the fact that they will only produce it in susceptible persons. I am quite sure that it is generally known that dangerous attacks of the disease are now rare. His suggested alternative of " tonsillitis " would certainly be more inaccurate. The patient with scarlet fever may have had tonsillectomy, and when the tonsils are present the inflammation is never limited to them. Also, tonsillitis may be due to organisms other than streptococci. I have never seen any statistical evidence as to the relative frequency of complications in other streptococcal throat infections as compared with scarlet fever from which it could be adduced that the liability is the same.

In doubting the necessity for routine penicillin treatment of all cases of scarlet fever, I do not intend to deny the immense benefit penicillin has been in the disease, particularly to patients who develop otitis media.

Waddon Hospital,
Croydon.

J. J. LINEHAN.

SIR,—Some of your correspondents seem to overlook that the notification of scarlet fever is a legal duty. The law may or may not be an ass, but it ought to be obeyed ; it is not for the private citizen to select which laws he will obey and which he will not. That way lies chaos. Provided that medical officers of health have a reasonable interest in watching the incidence of infections due to hæmolytic streptococci, the notification of cases of scarlet fever is not as foolish as it seems. It is a well-defined syndrome, and from most cases hæmolytic streptococci can be recovered ; whereas " sore thr is difficult to define, and its bacteriology is variable.

Giggleswick, Settle,
Yorks.

D. P. LAMBE

RESEARCH IN REGIONAL HOSPITALS

SIR,—After a previous letter [1] on this subject I had a number of inquiries and comments from different parts of the country. It is clear that few in regional hospitals realise that the free money—endowment fund or amenity fund, as it is variously called—is available both for amenities for patients and staff and for medical research. Even when this is appreciated, it may be felt rather incongruous to ask the hospital management committee consecutively for two such items as a hair-dryer for the nurses' home and a Geiger counter.

A local research fund, however, may be organised in two ways. Either a hospital management committee may form a special research account within its endowment fund, or a special research fund may be organised under trustees. This has the advantage that donors may feel that their gifts are removed entirely from Ministerial control. In one hospital this arrangement was required by a research corporation, which would otherwise have discontinued its grant after the Appointed Day. At my hospital there is a research fund, and recommendations for expenditure go from the medical advisory committee to the H.M.C.

Such funds may be financed by grants from the hospital endowment fund, from donations from patients' or from the public, or from fees paid to medical staff. Some whole-time staff may feel it is more appropriate for certain monies to be paid into such a fund than to be retained by the individual and mulcted by the Inland Revenue. Such monies may include capitation fees for nurses' medical care and fees for insurance reports, cremation certificates, and so on, much of this work, of course, being done during normal working-hours. In this way it is possible to build up a small, but very useful, research fund, and from this fund the purchase of special apparatus or payment for additional clerical or technical assistance may be sanctioned within a month, whereas normal channels for extraordinary expenditure may mean a delay of a year or even longer.

The purpose of such local research funds must be clearly defined. They can aim to facilitate small growing-points of knowledge in the regional hospitals. Once these growing-points have begun to flourish, they can be developed on a larger scale either by a regional research committee, the Medical Research Council, or a medical research foundation.

Department of Gastro-Enterology,
Central Middlesex Hospital,
London, N.W.10.

F. AVERY JONES.

SKIN REACTIONS TO ADHESIVE DRESSINGS

SIR,—I read with interest your annotation on this subject last week.

Adhesive bandages or strappings are being increasingly used in surgical and medical procedures because of their convenience, effectiveness, and stability as dressings. They are used in first-aid to hold dressings on operation wounds, and especially in the ambulatory treatment of chronically ulcerated legs.

Unfortunately a small proportion of patients ar sensitive to adhesive strappings and suffer pain, itching and skin eruptions from their application. Such symptoms are induced more quickly by strappings which owe their adhesiveness to a rubber-zinc " spread." These are more liable to cause reactions than those whos stickiness derives from a " spread " of lead, soap, and resin—i.e., the old-fashioned emplastrum saponis. 'Diachylon' and 'Lestroflex' are good examples of this second type. They are more tacky than thos of former days. All types of strappings tend to make their wearers hot in the summer, and in the winter cause itching and pustular eruptions if the patient continuously sits close to the fire.

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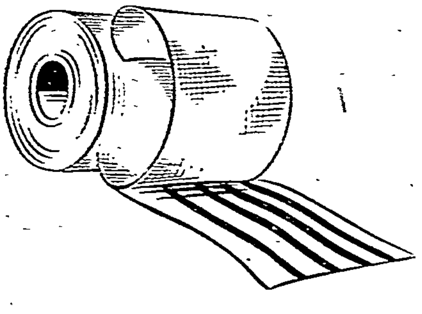
[1] Jersild, T. *Lancet*, 1948, i, 671.

[1] *Lancet*, 1951, i, 961.

Since the winter of 1950–51, I have used "ventilated" lestreflex and 'Dalzoflex' strappings (the latter has a rubber-zinc "spread"). These have proved singularly useful in the outpatient department and operating-theatre. The ventilation is achieved by applying the "spread" in separate strips ½ in. wide, separated by ⅛ in. gaps of uncovered bandage through which air and discharge can pass freely. This ventilation has the additional advantage of making the plaster more extensible and flexible than the fully spread ones. Patients who have experienced both types speak appreciatively of the coolness and comfort of the new preparations.



Ventilated dalzoflex is convenient for holding the gauze over the wound of a laparotomy, herniorrhaphy, saphenous ligation, appendicectomy, &c., although admittedly patients are occasionally sensitive to it. Ventilated lestreflex (soap, lead, and resin spread and less sticky) is very successful in chronically ulcerated legs. The adhesive surfaces of these two strappings have been cultured and found to be sterile, so that they are "safe" surgical dressings.

I am indebted to the research department of Dalmas Ltd., Leicester, for preparing and supplying this promising variation of strapping bandages.

London, W.1. HAROLD DODD.

DIABETIC ACIDOSIS WITHOUT KETONURIA

SIR,—Dr. Henneman's interesting description of a case under the above heading, in your issue of April 19, merits critical examination, and cannot be accepted as a proven example of diabetic coma without ketonuria.

Air-hunger can readily be produced by renal acidosis, and his case-report includes no mention of the presence or absence of albuminuria or the results of tests of the adequacy of renal function. Besides this, the necropsy showed sufficient cause for death and dyspnœa without invoking diabetic acidosis, suggested only by the acetone smell in the breath. Without a test for ketone bodies in the plasma—simple enough with Rothera's reagents—a determination of the alkali reserve, and a report on the presence or otherwise of oliguria or anuria, we do not consider that hyperglycæmia alone proves his thesis. Further, the pulse-rate, blood-pressure, and temperature are unlike those found in a patient dying in diabetic ketosis.

It is the general opinion that ketonuria is only absent in diabetic coma in patients with renal block; and as regards the rare exceptions reported in the literature and quoted by Dr. Henneman, it is very doubtful whether they were indeed true cases of diabetic coma. An English publication [1] dealing specifically with the subject of diabetic coma without ketonuria was omitted from his review of the literature.

Somewhat similar deaths in diabetics have been seen in this department, but were not reported because of the obscurity of the condition. But we cannot accept the suggestion that a diabetic without ketonuria and ketonæmia should be urgently treated with heavy doses of insulin before the diagnosis is accurately known. Diagnosis and treatment of diabetic coma on insufficient evidence may obscure the real ætiology of the patient's condition and lead to disastrous results.

R. D. LAWRENCE
W. G. OAKLEY
M. MENCER MARTIN.

Department of Diabetes,
King's College Hospital,
London, S.E.5.

INCOMPATIBLE TRANFUSION UNDER ANÆSTHESIA

SIR,—It has been said that anæsthesia masks transfusion reactions; and Muirhead [1] suggests that "the larger quantities of blood received make the cases serious." Cases in which large volumes of incompatible blood have been given without serious result have been reported; and Dr. Discombe (April 12) shows that even post-transfusional anuria is not necessarily associated with a high mortality.

In contrast, the following case illustrates that under anæsthesia signs of incompatibility can appear, and that small quantities of blood can cause a rapidly fatal result. The error was human, as in 70% of Dr. Discombe's cases.

A controlled diabetic man, aged 63, was to undergo partial cystectomy for a large diverticulum of the bladder. Preoperatively his blood was grouped, and three bottles of group-B Rh-positive blood was cross-matched. Premedication with 'Omnopon,' scopolamine, glucose, and insulin was satisfactory. Induction was with thiopentone (0·4 g.) and *d*-tubocurarine chloride (15 mg.); anæsthesia was maintained with nitrous-oxide oxygen (70–30%) and intermittent pethidine (25 mg. doses). The patient was 15° head-down, and respirations were assisted for 30 minutes. Blood-pressure (120/75 mm. Hg) and pulse-rate (60–65 per min.) remained steady for 2 hours, after which time the operation was being successfully terminated.

The surgeon asked that a transfusion be started to cover the loss of ¾–1 pint. An intravenous drip was set up at the wrist by the anæsthetist. While this was being strapped in place the patient's colour assumed a mild dusky cyanosis. A quick check showed respirations regular and strong and airway clear. The anæsthetic mixture was quickly changed and gradually increased to 100% oxygen, but cyanosis increased. The blood-pressure became unrecordable and no radial or carotid pulse could be felt, although the surgeon found a slight pulsation in the pelvic vessels. The anæsthetist stopped the drip, of which 70–100 ml. had been transfused, on a diagnosis of incompatible blood. Controlled respirations with 100% oxygen restored the patient's colour, and this measure was continued while the operation was concluded. Intravenous injections of nikethamide and 'Methedrine' were without effect. A slow infusion of noradrenaline produced a return of radial pulse, and the blood-pressure rose to 40 mm. Hg. By now the patient's blood had been re-grouped correctly as group-O Rh-positive, and a transfusion of compatible blood was commenced; but the patient's condition rapidly deteriorated, and he died within 2½ hours of the initial transfusion.

Necropsy showed no characteristic changes apart from acute hæmolysis and possibly vascular hæmagglutination in the cerebral capillaries.

Though the characteristic clinical signs were naturally absent in this patient, the sudden unexplained cyanosis, hypotension, and peripheral circulatory failure, associated with the commencement of transfusion and unassociated with other immediate signs of medullary depression, incriminated the blood. The maintenance of a constant level of anæsthesia and an undepressed vasomotor centre enabled the signs to be immediately recognised as not due to the anæsthetic, though unfortunately in this case the severe and rapid collapse was irreversible. In retrospect it would have been advisable to postpone the transfusion until consciousness, with the possibility of evident pyrogenic and hæmolytic reactions, returned in full; and a slower initial drip might have been possible.

Resuscitative intravenous therapy is a well-recognised part of the anæsthetist's responsibility. His vigilance should be an additional check against the occasional human errors which may occur, and which transform transfusions into potentially lethal procedures.

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[1] McCance, R. A., Lawrence, R. D. *Quart. J. Med.* 1935, 4, 53.

[1] Muirhead, E. E. *Surg. Gynec. Obstet.* 1951, 92, 734.

Queen Alexandra Hospital,
Cosham, Portsmouth.
R. J. HAMER HODGES.

CROSS-INFECTION IN THE WARDS

SIR,—I was interested to read in the *Times* (April 22) that the risk of cross-infection in hospital wards is now being investigated. Perhaps my own personal experience in a hospital is relevant.

In August, 1950, I entered a hospital to have my baby. After the confinement I was installed in a ward, with about 8 other patients, in which our 8 babies also slept at night and spent quite a large part of the day. Flies and similar insects invaded the ward and buzzed around the beds and the babies' cots. Most of the patients acquired cards impregnated with D.D.T. to help deter them, but the insects were persistent and it was impossible to rest peacefully during the day.

Having spent a short time in Singapore, where efficient D.D.T. spraying has almost completely destroyed insect pests, I wondered why similar methods on a smaller scale could not be used in British hospitals. On finding a dead fly in my lunch one day I mentioned the matter to a member of the group hospital committee, who was indignant at being bothered with such a trifling complaint, and retorted that there was nothing one could do about flies. I suggested fine mesh at the windows, if spraying proved inadequate; and he replied that that would keep out fresh air, and that in any case there were no funds to make such a provision. The sister tutor informed me that she had fought a losing battle on the same subject, and volunteered the information that a sewer not far away was the cause of the fly invasion.

Langley, Bucks.
RUTH GEARY.

VARICOSE ULCERS

SIR,—Your annotation of April 5 is timely, yet disappointing: timely in indicating the problem, and disappointing in underestimating present possibilities of treatment and organisation.

You emphasise the patient's attitude rather than the practitioner's need for reorientation and revision of ideas in meeting the problem of the ulcerated leg. Commonly patients "accept almost fatalistically" the presence of an ulcer because of past mismanagement and loss of confidence in medical treatment. Treatment should not consist in advising "a few weeks in bed." Leg ulcers can be healed quickly and efficiently with bandaging by the compression technique, and the patient remains up and about. To say that "nobody expects an ulcer in advance" is to ignore the experience of clinicians, such as Mahorner.[1] He calls for a long-term view of the œdematous leg, urging the need to visualise the march of a chronic process. He advises measures to reduce the œdema and emphasises that the indurated leg and recurrent patch of eczema should be regarded as links in a progressive series of events, the end-point of which is the ulcerated leg should preventive measures be unsuccessful.

The emphasis on varicose veins in the ulcerated leg is rejected by Anning[2] and Lockhart-Mummery and Smitham.[3] Varicose veins are not always associated with so-called varicose ulceration, and moreover many patients with gross varices never have ulcerated legs.

One should avoid rigid treatment either of the ulcer itself (whereby enthusiasm for local applications results in therapeutic dermatitis) or of the veins (with enthusiasm for injection, ligation, &c.). A combined dermatological and surgical approach is needed for a balanced appreciation of ætiology and management of the ulcerated leg.

The ulcerated leg should be taken out of the group of lost causes since these ulcers clear up very often without hospital treatment or loss of time to the patient. Special ulcer clinics aid the observation and management of such patients, and the patients, by observing others, improve and, noting the special attention given, get a much-needed psychological fillip, thus developing a more coöperative and helpful outlook.

The ulcer problem should therefore be relieved by (1) knowledge of the natural history and background of the ulcerated leg; (2) decreased emphasis on varicose veins; (3) measures to reduce œdema in the pre-ulcerative phase; (4) increased knowledge of the compression technique of bandaging, encouraged by attendance of practitioners at ulcer clinics; and (5) coöperation by surgeons and dermatologists to promote treatment, observation, and research.

Nottingham.
H. LEE.

INTRATHECAL AUREOMYCIN IN MENINGITIS

SIR,—I have read with interest the article by Dr. Ainley-Walker and Dr. Bosanquet in your issue of March 1, and the ensuing letters by Mr. Martinez (March 15) and Dr. Liversedge (March 29).

Ainley-Walker and Bosanquet showed in fifteen neurosurgical patients, who, implicitly, were not suffering from meningitis, that following heavy short-term oral dosage or single-injection intravenous dosage with aureomycin, "it was found impossible to obtain a therapeutic C.S.F. aureomycin level by giving aureomycin systemically." The single patient with meningitis to whom they gave aureomycin orally failed to respond until the subdural abscess which occasioned the meningitis was treated locally.

It seems to me that, however good a case Ainley-Walker and Bosanquet may have made for intrathecal aureomycin in meningitis, they have made no case against the use of systemic aureomycin, as the blood-brain barrier for the drug may be much lowered by the presence of the inflammatory reaction of meningitis. Their case 1 treated by oral aureomycin could hardly be expected to recover, if the first principle (vide Mr. Martinez) of treating the abscess cavity were neglected. This case, while tending to show that a "therapeutic level" of aureomycin cannot be obtained in the cerebrospinal fluid (C.S.F.) by systemic administration despite inflamed meninges, also raises the question whether the in-vitro determined therapeutic level bears any relation to the in-vivo requirement, as once the abscess was treated locally the meningitis recovered, although the C.S.F. level of aureomycin was only one twenty-fifth of the estimated required level (0·1–2·5 µg. per ml.).

The following case-history may not be without interest.

The patient, a European woman aged 54, was admitted to hospital with a history of a 5-day influenza-like illness. For 3 days before admission she had been treated by her family doctor with sulphadimidine, approximately 12 g. total dosage.

On admission she was found to have cerebrospinal meningitis, with numerous organisms present in a direct smear of the C.S.F. She was put on full doses of 'Soluthiazole' by injection and sulphadimidine orally, and penicillin 2 million units 6-hourly by injection. She responded at once, and after 72 hours the temperature was normal and the patient felt much better. On the 4th day of treatment she was not so well; her temperature had risen again, and she complained of severe pain in her lumbosacral region and thighs. On the 5th day of treatment her legs were so painful that they could scarcely be touched or moved. Lumbar puncture combined with strong aspiration produced a few drops of jelly-like C.S.F., which again showed the presence of diplococci on gram staining. 20,000 units of penicillin were given

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1. Mahorner, H. *Surg. Gynec. Obstet.* 1949, 88, 115.
2. Anning, S. T. *Brit. med. J.* 1949, ii, 458.
3. Lockhart-Mummery, H. E., Smitham, J. H. *Brit. J. Surg.* 1951, 38, 284.

intrathecally. On the 6th day the patient was extremely ill; lumbar puncture produced no fluid, the spinal block now being complete. The pain in the legs was intense, presumably owing to inflammatory exudate spreading along the spinal roots; the mental condition was clouded and confused. At this stage the patient, since admission to hospital, had received soluthiazole 5 ml. intravenously and 4 ml. intramuscularly, sulphadimidine 38 g. orally, and penicillin 46 million units by injection.

All these drugs were stopped; and since she was now incapable of swallowing, aureomycin three capsules (750 mg.) was given rectally every 6 hours, increasing to four capsules (1 g.) after three doses. Within 24 hours she showed some improvement and was taking fluids well, and from then on was given the aureomycin orally in the same dosage. She progressed to rapid and uninterrupted recovery on a total dosage of 26 g. of aureomycin.

This case-history shows that in a case of penicillin-resistant and sulphonamide-resistant meningococcal infection with spinal block, systemic administration of aureomycin may be life-saving; and it would be well worth extended trial in other forms of intractable meningitis.

General Hospital,
Bulawayo, Southern Rhodesia. J. CHARLES SHEE.

THE DENTISTS BILL

SIR,—In his letter of April 12, Mr. Breese refers to the starting of the first dental clinic in London.

This clinic was not started by a group of people but by Dr. R. A. Kirby, a retired Naval medical officer; and it was first established as a general dispensary in Broadwell, a turning out of the New Cut in Blackfriars, S.E. The work became so great that it was gradually restricted to children only, and I was attached to the dispensary from an early date as assistant to Dr. Kirby. In addition to being assistant I was also one of the first school medical officers appointed by the London County Council, whose chief medical officer (education) was Dr. James Kerr. The great mass of untreated *minor ailments in London revealed by medical inspections in* the schools led to the greater and greater specialisation of the dispensary on the ailments of school-children, and incidentally to its removal to its second home in Pocock Street, which Mr. Breese mentions. This was called by Dr. Kirby, the founder, St. George's Dispensary.

Among these ailments were carious teeth, which at that time it was not possible for the poor parents of Southwark to get treated except with the greatest difficulty. It was as the direct result of the setting up of the school medical inspection service under Dr. Kerr that the need for special clinics for treatment of the teeth was brought to light; and after a report by Mr. Wallace, at that time the only dentist employed by the L.C.C., Dr. Kirby undertook to have a room prepared, and a chair for dentistry specially made on a plan suitable for a children's dental clinic, after which Mr. Breese was appointed as the dentist. The beneficent results of the general school-clinic work, as of the dental clinic, were obvious from a very early date, and the movement to establish school clinics spread in London and eventually all over the country.

Dr. Kirby was a man of high ideals who wished to perform a useful social-service with money which he had inherited. I am glad to put on record this bare outline of the beginning of the school-clinic movement, so largely due to his idealism and desire to serve his fellow men. The original dispensary was called "St. George's Dispensary," not for any local reason, but because St. George is the patron saint of England and Dr. Kirby had set out to achieve good deeds for the people; and in Southwark in those days they were indeed poor and often wretched, and help was very badly needed.

Dr. Kirby retired from the clinic work some time between the wars, when it was at a new address in Blackfriars Road. We then set up a committee, of which I remained chairman until the clinic was handed over to public control on the coming in of the National Health Service.

House of Lords. HADEN-GUEST.

WHAT SHOULD THE NURSE BE TAUGHT?

SIR,—The letter from Dr. Cropper and Mr. Houghton has provoked much thought amongst nurses and reminds us again to reconsider the nurses' curriculum.

There is much in your leading article with which we agree, but the length of the training must depend on three main issues. First, what is the aim of the training? Your correspondents seem to think that a nurse is a being who exercises her calling solely inside a hospital ward, "the greater part of her training should be in the minutiæ of ward-management," implying that the required end-product is a good ward administrator. We are aiming now to break down the barrier that has enclosed the student nurse within the hospital ward and to include in the training health education and conservation, as well as bedside nursing and ministration to the sick. The education committee of the International Council of Nurses summarises the aim as that of teaching "The nursing care of the patient, mind as well as body; the care of his environment, social as well as physical; and health service to families and communities as well as to individuals."

The second issue is the ground to be covered during the training. This becomes increasingly difficult as advances are made in all branches of medicine. Your correspondents ask that the nurses' curriculum should be limited "to matters truly relevant to a nurse's duties." This is easier said than done. They add "anyone who has been warded knows that what the patient asks of the nurse is an indefinable quality of personality which makes her more than a technician." Can this kind of a nurse be trained by being taught "a circumscribed range of facts and techniques germane to the craft of nursing"?

Thirdly, it is important to consider whether the student nurse is admitted to the school to receive a training or is regarded as a necessary and cheap method of staffing the hospital. Unfortunately it appears that hospital committees are more and more thinking on these latter lines.

Your article points out that Florence Nightingale was able to teach bedside nursing procedures and good nurse-patient relationships in one year. In 1860 the nursing procedures were very limited and there was one new probationer, aged 25 or more, in a ward at a time. She could be truly apprenticed to the ward sister, and from 1872 onwards had organised instruction from the home sister as well as from the medical officer.

You also refer to the Canadian demonstration school in Windsor. There the students are not responsible for staffing the adjoining hospital. That hospital has never had a nursing school or student labour; therefore the director of the nursing training can arrange where the students work in the hospital, for how long, and how much instruction they need in order to acquire "these techniques and all the rest of the curriculum besides." Their curriculum includes experience in the maternity department, in a tuberculosis sanatorium, and in a psychiatric hospital. As you say, the students in that demonstration school are picked, and, besides, the staff are excellent teachers; but more important to the success of the scheme is the fact that the school has financial and educational independence. Only under these circumstances could the period of training be shortened.

An arbitrary change in the length or content of the curriculum will not solve our problems, but experimental schools might give us a better idea of possible lines to pursue. The 1949 Nurses' Act has sanctioned experimentation and allows the General Nursing Council to approve schemes put forward. Now is the time for action so that either we can defend our present system of training more realistically or we can gradually bring about a change. As long as the majority of student nurses are primarily engaged in staffing the hospitals and only secondarily being given a training, so long will we be tied to a rigid curriculum and be prevented from making progress.

Nightingale Training School,
St. Thomas's Hospital,
London.

R. A. HONE
Sister Tutor.

SIR,—I was sorry to read that Miss Ottley has nothing but condemnation for nurse cadet training schemes whether properly conducted or not. Nobody would disagree with her contention that these young girls should not be employed on nursing duties, but surely this is a reason for laying down and enforcing proper standards and not for abolishing all schemes good and bad?

The simple fact must be faced that a large and growing proportion of nurse students must come from girls leaving school at the age of 15. What is to happen to them until they begin nurse training at 18? Is it better to leave them to find employment in industry or commerce (where they will find higher salaries and greater excitement than in hospital) or to employ them as cadets in hospital for four days a week and send them to school to continue their general education?

A study of the literature shows that wastage is, and has been, high among student nurses from whatever source; and few properly conducted cadet courses have been running long enough for much experience to be gained.

The sister tutors' section of the Royal College of Nursing reported recently on the poor knowledge of arithmetic found generally among student nurses. In my group we find the education authority most willing to arrange a syllabus of teaching, paying special attention to weaknesses of this kind.

A large modern hospital is a complex collection of departments surrounding the focal point which is the ward. Unfortunately, the complexity has grown so much that few nurses have any appreciation of what goes on in more than one or two departments. A spell of a few months as a junior helper in most parts of the hospital surely helps an intelligent girl to become a more useful member of the hospital staff. Those of us in non-teaching hospitals, with the problem of nurse recruitment constantly with us, have given much thought and care to founding cadet courses with the aim of improving the quality and quantity of our future students. We shall need more evidence than Miss Ottley presents to be convinced that we are completely wrong.

Rochdale and District
Hospital Management Committee.

S. HODKINSON
Group Secretary.

NERVOUS CONTROL OF SWEATING

SIR,—Your most interesting annotation last week explains clearly the mechanisms at work in hyperidrosis. It is stated that Chalmers and Keele [1] found the excessive sweating of hyperidrosis to be due to the increased release of acetylcholine at the postganglionic nerve-endings, and this release was most probably due to an increased central nervous activity. In support of this contention I would like to describe the following case.

A boy, aged 13, was sent to me from the skin department with a history of excessive sweating of the hands and feet. The condition had appeared suddenly. If the patient wiped his hands, drops of sweat appeared immediately and fell freely from the fingers. All manner of treatments had been tried without result. The condition first started when he was evacuated during the war; he was then 8 years of age. He remembered that his hands were quite dry before he left home.

Under deep hypnosis he was regressed to the age of 8 and was able to remember incidents on his first day at the new school. On the way to school he was attacked by a gang of boys, who shouted anti-semitic slogans at him; eventually the gang set on him and beat him up. He became acutely tense while reciting these incidents. On being awakened he remembered the fighting, and stated that he had felt he would have liked to "murder all of them" but was too terrified to hit back because there had been too many against him. He said he thought they were going to murder him. He was abreacted on three more occasions. After seeing me at six sessions he is now no longer conscious of his hands and feet; he can do his school-work without the sweat pouring over his books, and has remained well, without relapse, for over one year.

Here is a case in which pathological sweating was cured by seemingly cutting off the acetylcholine producing the hyperidrosis. Yet, as you remark in another annotation last week (p. 862), the value of injecting acetylcholine bromide in anxiety states with tension is being investigated. Professor Lopéz-Ibor, to whom you refer, might label my case a "timopathic disorder" and inject acetylcholine intravenously.

I can only suppose that the giving of acetylcholine causes an "explosion" of the fear and tension holding the anxiety together (much after the fashion of a fit induced by electroconvulsive therapy). I would imagine that any substance producing physiological shock would give the same result. I would be most interested in any other explanation.

Prince of Wales's General Hospital,
London, N.15.

GORDON AMBROSE.

BOVINE TUBERCULOSIS PREVENTS HUMAN TUBERCULOSIS?

SIR,—Dr. McKinstry (April 19) refutes my statement that the incidence of tuberculosis is increasing in Jersey by the odd explanation that the mortality-rate is falling. Surely the fall in the death-rate is due to treatment by new methods (or perhaps death is being deferred). The death-rate is as high in Jersey with 100% cattle attested as it is in England with 20% cattle attested.

As I have shown (April 12), the infection-rate is very materially increasing in Jersey. The tuberculosis position there roughly corresponds with that in the Scottish counties with a high percentage of attested cattle.[1] To say that increased care is being taken of tuberculous patients appears to me to be a corollary to the fact that there is very much more tuberculosis to be taken care of. It has been rightly said that the true measuring rod of tuberculosis is not the death-rate but the number of sick people. Death from tuberculosis is a consequence of infection.

High Wycombe, Buckinghamshire.

L. PITCHER.

SIR,—Mr. Pitcher's faulty interpretation (April 12) of the Jersey tuberculosis figures should not cause us to forget his service in pointing out the general inverse ratio between the incidence of bovine tuberculosis and the death-rate from all forms of tuberculosis. His figures for the whole of Scotland have been supported in detail for Ross [2] and for Kilmarnock.[3] A similar trend for England and Wales was reported by Francis,[4] who records two Danish observations [5] [6] of the same phenomenon. A further illustration is provided by the report of the M.R.C. National Tuberculin Survey, in your issue of April 19. This shows a high incidence of infection in rural populations, where there is a low tuberculosis death-rate and the consumption of raw tuberculous milk is highest.

Although it is difficult to accept Mr. Pitcher's explanation, there seems little doubt that a significant inverse ratio exists. He concludes, however, that in the absence of a satisfactory vaccine the attempt to eradicate bovine

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1. Chalmers, T. M., Keele, C. A. *Brit. J. Derm.* 1952, 64, 43.

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1. Pitcher, L. *Lancet*, 1951, ii, 786.
2. Horne, J. L. *Ibid*, p. 1228.
3. Nisbet, B. R. *Ibid*, p. 1090.
4. Francis, J. *Ibid*, 1950, i, 34.
5. Holm, J., Holm, H. *Acta tuberc. scand.* 1945, 19, 71.
6. Madsen, T., Holm, J., Jensen, K. A. *Ibid*, 1942, suppl. no. 6.

tuberculosis is futile. It is here that physicians must take issue with him:

1. The estimated annual death-rate from infection with the bovine bacillus in Great Britain is between one thousand and two thousand.[7] This is too high a price to pay for the immunising value of tuberculous milk.

2. Eradication is necessary on economic grounds alone. It is estimated that the disease costs the country £1–3 million per year by loss of milk output and condemnation of meat.[7]

3. Although B.C.G. is of no value as a veterinary vaccine, it is satisfactory in man.

The ultimate aim in this country must be to eradicate tuberculosis from man and animals; but this state of affairs seems to be far distant, and it is safer in a heavily infected community to be Mantoux-positive. The need, therefore, is for the continued elimination of bovine tuberculosis accompanied by a full-scale attempt to immunise susceptible people.

Altrincham, Cheshire.   R. M. FORRESTER.

JOINT-STRAIN IN SLEEP

SIR,—Your annotation of April 12 opens with the statement: "As long as we are up and doing, our joints are kept nicely in the true, not only by their ligaments but also by the tone of neighbouring muscles." This statement will not be endorsed by anyone who is experienced in the F. Matthias Alexander technique.

It is over fifty-six years since Mr. Alexander made the observation that, in reacting in accordance with the dictates of instinct, most persons employ a use of the self which is associated with a debauched standard of sensory appreciation. Lacking reliable sensory guidance, they use the self in a way which maladjusts it as a whole. The maladjustment thus induced impedes the working of what Mr. Alexander has called "primary control"—the control which Nature designed to have an integrative influence on the working of the self. Now a person who reacts by instinct puts undue and uneven pressure on his various joints, thus interfering with their best working and even with their natural construction. It is only when a person has gained experience in the use of the Alexander technique and has thus learned to withhold instinctive reaction, and to use in its place conscious guidance and control of reaction through a properly understood use of primary control, that he is able to improve his self-awareness and, therefore, his means of recognising that what he originally felt and believed was a good use of the joints was really a very bad use.

A person who inhibits his immediate reaction to a stimulus, and thereby, indirectly, consents to primary control operating without interference, is thus enabled to let the head go forward-and-up, the neck to be free from tension, the back to lengthen and widen, and the upper and lower arms, the upper and lower legs, the hands, fingers, and thumbs, and the feet and toes to diverge in the greatest possible degree from the parts to which they are joined and thus immediately related. In this way he is able to adjust the self so that the muscular tension is the least possible throughout, and therefore to create circumstances in which all the joints are adjusted in a manner which might be described as "in the true."

A joint or any other part is "in the true" only when a person, having adjusted the self by a correct employment of the integrative principle of primary control, employs a use of the self in accordance with that principle.

Bolton, Lancs.   MUNGO DOUGLAS.

SIR,—From your annotation it would appear that you may not have had time to glance at the chapter on "Sleep and its Disturbances," in *Recent Progress in Psychiatry*, 1950, in which McDonnell's article was discussed. According to him, many symptoms and painful disabilities, such as intercostal neuralgia and so on, result from a faulty sleep posture assumed by a large proportion of the population who, according to him, do not know how to lie in bed. He says that rotation of vertebræ, a widening of the costovertebral ligaments, and irritation of intercostal nerves are responsible for many painful disabilities. His views are not supported by the experience of thousands of Londoners who during the war years slept in overcrowded underground railway stations, in air-raid shelters, and in Anderson shelters. Elderly persons slept in armchairs. There was both objective and subjective evidence that many slept soundly in spite of uncomfortable postures. Yet there is neither clinical nor statistical evidence that the incidence of painful disabilities such as those mentioned by McDonnell has appreciably increased as a result of the faulty posture assumed by these people.

Belmont Hospital,
Sutton, Surrey.   M. N. PAI.

SELF-DEMAND FEEDING OF INFANTS

SIR,—Dr. Wallace (April 19) sets out to extol the merits of an elastic feeding schedule for infants at the expense of the self-demand method. If a baby's routine is to be determined neither by the clock nor by its own intrinsic pattern of feeding behaviour, what is to regulate it? Is the baby to be roused from sleep because the mother would like to be done with one item of the day's work before she gets on with another—or left to cry with hunger for half an hour while she prepares a meal?

Most mothers, if left to their own devices and freed from the oddly stern attitude imposed by many well-meaning welfare clinics, would pick up their baby when it cries and feed it when it shows signs of hunger. Nothing increases maternal confidence so much—I speak from experience—as the knowledge that the baby's needs can be correctly interpreted and dealt with as they arise. Why should any arbitrary standards of management be allowed to interfere between the two?

Young mothers do need advice; they like to be given positive directions and encouragement; they need to feel that they are competent. The simplest feeding advice that could be given to any woman with her first baby would surely be: "Watch him and see how he behaves when he's hungry; and when he's hungry feed him." This is, after all, the only rule observed by many mothers in civilisations simpler than our own; and their success in breast-feeding suggests that it is sound.

Monkmoor Hospital,
Shrewsbury.   ALISON NEVILLE.

THE PRACTITIONER'S PRESCRIPTIONS

SIR,—Dr. Andrew Topping, dean of the London School of Hygiene and Tropical Medicine, is reported to have told the annual congress of the Royal Sanitary Institute that "unscrupulous patients made no secret of the fact that they would transfer to another doctor if not given a certificate, put off work, or given the variety of medicine they themselves considered advisable. That there were comparatively few transfers showed how very rarely the practitioners refused. Compliance was the easiest way out, and consciences soon got hardened."

Are the general practitioners of today really such a weak crowd as Dr. Topping makes out? Do we really give our patients fancy medicines which they do not need for fear that they change their doctors? Do we give them untrue certificates for the same reason, and if we do not pander to their whims do they go elsewhere? If we can believe some of the more sensational papers this is the rule, not the exception.

In my experience few patients change because we refuse unreasonable requests and those who do are often ones who have gone the round of doctors, and are best off our lists anyhow. My patient who asked for a bottle of 'Dettol' "because I always bath in dettol" did not go elsewhere because her request was refused, but handed me her newborn baby's card instead. I am sure that the sensible, honest, big majority of the community do not go about changing their doctors without a good reason. But if the daily press continues to paint us as a set of unscrupulous unit-grabbers and we do nothing to repudiate this, the general public will in time get this impression, too, and treat us as such.

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[7] Francis, J. Bovine Tuberculosis. London, 1947; p. 183.

Exmouth. ARMOREL NETTELL.

CŒLIAC DISEASE

SIR,—I have read with much interest last week's paper by Dr. Anderson and her colleagues and your leading article. We, at this hospital, where there are a number of children with the cœliac affection under treatment, first became interested in Dicke's work on this disease when he brought it to the notice of pædiatricians at the sixth International Congress of Pædiatrics in Zürich in 1950. Our interest became practical when Dr. Dicke visited England and Manchester in 1951. A result of his visit was the devising of a diet-sheet which formulated a suitable diet for the cœliac child; this diet excludes wheat flour and gluten, as had been recommended by Dr. Dicke. The parents of the child with cœliac disease were also given instructions by the hospital dietitian (Miss Joan Waring) on the making of bread free from these vegetable products. The results have been as good as those reported.

One clinical feature which is mentioned in the paper but which should be further emphasised—for it means so much to the parents—is the remarkable improvement in the temperament of these children within days following the exclusion of the wheat flour and gluten from the diet.

Duchess of York Hospital
for Babies, Manchester. THEODORE JAMES.

PATHOLOGY OF BRACKEN POISONING IN CATTLE

SIR,—Your leading article of Jan. 19 has overlooked the fact that bracken poisoning in cattle cannot be regarded simply as a B_1-deficiency disease. Furthermore "staggers" does not appear in cattle. Sun drying does not necessarily destroy the thiaminase.

The essential lesion in cattle is extensive bone-marrow damage. Thrombocytopenia and leucopenia result, and are followed by extensive hæmorrhages (Naftalin and Cushnie[1]). A few days before death the body-temperature is elevated from its normal in cattle of 102°F up to 107°, and this coincides with a non-specific bacteræmia.

Accounts of recent work in this institute are being prepared for publication.

Rowett Research Institute,
Bucksburn, Aberdeenshire. J. M. NAFTALIN.

CORONARY AND MYOCARDIAL DISEASE

SIR,—In his letter last week, anent Dr. Logan's paper of April 12, Dr. Harrison states that, unless he is mistaken, the certified causes of death from coronary disease including angina pectoris, and myocardial and cardiovascular degeneration, "all refer to the same pathological entity—namely myocardial ischæmia due to coronary atherosclerosis." Sir, Dr. Harrison is mistaken.

Myocardial or cardiovascular degeneration is the cause certified by clinicians in the absence of clinical evidence of the major forms of coronary artery disease, angina pectoris, coronary thrombosis, myocardial infarction, et sequelæ.

As commonly employed, myocardial or cardiovascular degeneration may denote one of three conditions:

1. It may signify death in the aged, in conjunction with bronchopneumonia, in whom the changes are those of ageing alone and in whom there may be no evidence of fibrosis resulting from arteriosclerosis or arteriosclerosis with atheroma; for usually the heart continues to hypertrophy and increase in weight steadily through the years even in the uppe end of the octave of life.

2. Myocardial degeneration alone is certified, too, in cases in which the heart shows either little or no loss in muscle-bulk but is brown as in brown atrophy; and the term is used also to signify the latter pathological state.

3. Cardiovascular degeneration, as opposed to myocardial degeneration, is used to indicate the terminal event or stage of heart-failure in hypertension or in arteriosclerosis, and is usually coupled with these terms.

And so, vague and inexact though they be, cardiovascular and myocardial degeneration do mean something clearly distinct from coronary arterial diseases and their immediate and remote sequelæ.

Department of Pathology,
North Middlesex Hospital,
London, N.18. J. F. HEGGIE.

RADIOLOGICAL INVESTIGATION

SIR,—I was interested to read Dr. Brailsford's defence of his thesis (April 26). There are portions of his letter with which I cannot agree.

In his first paragraph he argues from the particular (the Army) to the general—fundamentally a bad principle. My experience in the late war is completely different from that of Dr. Brailsford; radiological facilities were available and were used.

I think he would find very few doctors to agree with him that a patient could have the signs and symptoms of pulmonary tuberculosis without any radiological evidence of the condition.

Dr. Brailsford goes on to suggest that he is surprised that any of the cases in my series had signs and symptoms. It seems to me that there is a weakness in his argument. I quite agree that in using mass miniature radiography to examine cases referred by general practitioners there will be a high yield of active cases of pulmonary tuberculosis. But it is as well to note that these patients are already reporting with symptoms; patients who have symptoms have in the vast majority of instances got extensive disease.[1] It is quite possible that many of the cases discovered by mass radiography and contact examination will prove eventually to be quiescent. This can only be substantiated by 3-5 years' observation. Many workers believe that if these cases break down they do so within the first two years.[2,3] My experience has been that there is still an appreciable number of breakdowns even after two years.

I do not believe that it is possible to estimate from the radiological characteristics whether or not an individual case is going to relapse, and in this I am in agreement with Daniels[2] and Aspin.[3] I certainly agree that many of the cases of pulmonary tuberculosis will heal without treatment. But until either the radiologist or the clinician is in a position to distinguish those cases which are going to take such a favourable course from those which are not, all these cases must be followed up carefully.

There is still a great deal to be discovered about pulmonary tuberculosis, and we shall not advance our knowledge by confining ourselves to the patients found in the waiting-rooms of general practitioners.

Dr. Brailsford's final paragraph I found very difficult to understand. No responsible clinician treats cases of pulmonary tuberculosis by means of surgery or by temporary collapse therapy unless he has got clear indications of activity.

Dr. Brailsford still does not convince me that a history and a stethoscope are the most reliable means of identifying active pulmonary tuberculosis before it has become a major therapeutic problem.

René Théophile Laennec wrote in 1819[4]: "Small tubercles separated from one another by portions of healthy lung cannot be recognised. But at this period of their progress the health is commonly still good and the cough too slight to induce the patient to consult a medical man."

Liverpool. PETER O. LEGGAT.

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1. Naftalin, J. M., Cushnie, G. H. *Vet. Rec.* 1951, 63, 332.

1. Simon, G. *Brit. J. Radiol.* 1943, 16, 217.
2. Daniels, M., Ridehalgh, F., Springett, V. H., Hall, I. M. Tuberculosis in Young Adults. London, 1948; p. 163.
3 Aspin, J. B. *Tubercle*, 1949, 30, 170.
4. See Paxon, T. *Lancet*, 1950, ii, 769.

Parliament

National Health Service Bill

On April 23 a Government motion was passed to apply the system of closure by compartments, popularly known as " the guillotine," to the remaining stages of this Bill. Under this procedure a restricted amount of time is allotted for the discussion of a clause or a group of clauses, or a particular stage of a Bill, and at the end of this time all remaining amendments, except Government amendments, are ruled out. The Government motion proposed that the remaining stages of the National Health Service Bill should be completed in two days, one of which should be allotted to the remainder of the committee stage and the other to the report stage and third reading.

When the committee stage was resumed on April 24 Mr. Hector McNeil moved an amendment to provide that people falling under the National Insurance Acts should be exempted from the charges under the Bill. Miss Patricia Hornsby-Smith said that the Government considered that the new non-contributory arrangement could not fairly be compared with the old contributory one. For one thing the old benefits were for the insuree alone ; the new benefits covered his family. Mr. McNeil's amendment was negatived.

In the debate on clause 1 Mr. J. E. Powell said that he thought the Minister was right to set his face against any type of exemption. We could not draw a boundary line, on one side of which there is hardship and on the other side there is not, by trying to define the type of case. Only by finding where hardship in practice arises in individual circumstances could the impact of the charges where necessary be alleviated. The regular necessity of paying the prescription charge might cause hardship, but it would do so, not because of the chronic nature of the sickness, but because of the circumstances of the patient. Mr. Aneurin Bevan was attracted by the proposition that if public authority is to intervene between a citizen and the vicissitudes of life and the circumstances of the market the individual should establish his claim to assistance. But he thought it ought to be applied to all. For instance, should not the farmer go to the National Assistance Board and establish his claim before benefiting from the fertiliser subsidy ?

When the guillotine fell the motion that clause 1 stand part of the Bill was carried by 305 votes to 285.

THE REMAINING CLAUSES

On clause 2 Mr. H. F. C. Crookshank moved an amendment to exclude from any charge the clinical examination which a dental patient might have and the report on it. He hoped that this would encourage people to consult their dentist more often than if they had to pay for an examination. The amendment was agreed to.

Mr. H. L. Marquand moved an amendment to exclude a service for which the fee was not more than £1. The patient who neglected his teeth and only visited the dentist rarely would pay a smaller proportion of his treatment than the patient who attended regularly. But Mr. Crookshank pointed out that if the first £1 worth of dental work was free of charge there would be a strong inducement to patients to have only part of the necessary treatment done at one time. The amendment, if carried, might mean the loss of the greater part of the estimated saving of £6 million a year. The amendment was negatived by 303 votes to 283.

On clause 3 Sir Edward Boyle moved an amendment to ensure that if any Government wished to increase these charges they should do so by bringing a fresh Bill before the House. Mr. Crookshank accepted this amendment.

In the debate on clause 5 Mr. John Wheatley asked what justification there was for the new principle of penal sanctions against the people in the health service. Mr. Crookshank replied that they were trying to make the collection of charges as simple as possible. Lest dishonest people took advantage of this, some effective punishment was provided.

Mr. Somerville Hastings moved an amendment to clause 6 to ensure that money collected from patients should be ploughed back into the N.H.S. But, under the guillotine procedure, there was no time to discuss it. A new clause was passed giving power to remit charges for dentures supplied by teaching hospitals, and the committee stage of the Bill ended.

QUESTION TIME

N.H.S. Prescriptions

In answer to questions Mr. James Stuart stated that the number of prescription forms dispensed in Scotland in the twelve months from April, 1951, to March, 1952, was 14,800,000, representing over 20½ million prescriptions. The approximate average cost per prescription was 3*s*. 6*d*. in the second half of 1948 ; in 1949 it was 4*s*. 1*d*., in 1950 4*s*. 4½*d*., and in 1951 4*s*. 7*d*.

In answer to a question Mr. H. F. C. Crookshank stated the number of prescriptions dispensed in England and Wales in the year ended Dec. 31, 1951, was approximately 228·6 million.

Wigs and Surgical Appliances

In answer to a question Mr. Crookshank stated that the following numbers of appliances had been supplied in England and Wales since the N.H.S. started :

Year	*Wigs*	*Abdominal belts*	*Pairs of boots*	*Pairs of hosiery*
1948–49 ..	3977	97,469	16,760	14,140
1949–50 ..	12,398	156,868	43,381	28,280
1950–51 ..	11,751	115,354	44,623	34,137
1951–52 .. (nine months)	6288	73,057	33,479	26,294

Surgical Appliances for Outpatients

Mr. Somerville Hastings asked the Minister of Health whether he was aware that hospital outpatients awaiting the delivery of surgical appliances had been asked to sign a declaration that if the National Health Bill, 1952, becomes law before delivery they would agree to pay whatever charges become payable ; and if, in view of the fact that when the National Health Service Act, 1946, came into operation hospitals honoured arrangements previously made with patients, he would see that patients were similarly treated in this case.—Miss Patricia Hornsby-Smith replied : As the Minister stated on the second reading of the Bill, it is proposed that under the regulations under clause 1 charges will be payable for appliances supplied after the operative date of the regulations ; and the Minister has suggested to hospitals that, in fairness to those concerned, they should warn patients of the position which may arise.

Medical Rejection of Service Recruits

Replying in the House of Lords to Lord Kenswood, Lord Lloyd said that about 17% of class G recruits and 18% of class Z reservists were eliminated on purely medical grounds.

Public Health

Statistics for the First Quarter

The Registrar-General[1] announces the following provisional figures for England and Wales in the quarter ended March 31 this year (corresponding figures for the same quarter last year in parentheses) : birth-rate 15·9 (16·3) per 1000 population ; stillbirth-rate 23·3 (23·6) per 1000 total live and still births : death-rate 13·5 (19·1) per 1000 population ; and infant-mortality rate 33·4 (38·2) per 1000 related live births—the lowest rate yet recorded in a March quarter.

Vaccination and Immunisation in Lancashire

In his report for 1950 the county medical officer of health for Lancashire gives figures which show a very considerable increase in the numbers of both primary vaccinations and revaccinations as compared with those for 1949. Primary vaccinations increased by nearly 58% and revaccinations by over 120%. The total of diphtheria immunisations, on the other hand, fell ; primary immunisation at ages under 5 declined by nearly 18%, and at ages from 5 to 14 the reduction was 36%. Reinforcement injections also fell by more than 30%. The report notes that " this disturbing trend . . . was particularly marked in the second half of the year." In previous years most immunisations have usually been performed in the second six months of the year, and the decline in 1950 "is therefore all the more striking."

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[1] Registrar-General's Return for the Week ended April 19. H.M. Stationery Office. Pp. 20. 1*s*.

Precautions Against D.N.O.C. Poisoning

The Ministry of Agriculture and Fisheries have announced a plan for the early detection of poisoning by dinitro-*ortho*-cresol (D.N.O.C.) among agricultural workers. D.N.O.C. is used to keep down weeds in cereal crops; it is a cumulative poison and 8 fatal cases have been recorded since 1945 among those manufacturing or spraying it. The routine estimation of D.N.O.C. in the blood can be used to prevent serious poisoning.[1] [2] Under the Ministry's voluntary scheme, contractors engaged in large-scale spraying will appoint medical practitioners who will examine the exposed workers and take samples of blood when necessary. Certain pathological laboratories are equipped to carry out the examination, and a list of these will be sent to the doctors concerned.

Variola Minor in South-east Lancashire

No notification of variola minor was received from south-east Lancashire in the week ended April 26. The last reported case in the area was removed to a smallpox hospital on April 17.

Variola Major

A patient with suspected modified smallpox was removed from a ship at Swansea on April 23 and admitted to a smallpox hospital for isolation and further investigation.

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1. Bidstrup, P. L., Bonnell, J. A. L., Harvey, D. G. *Lancet*, April 19, 1952, p. 794.
2. Harvey, D. G. *Ibid*, p. 796.

Appointments

ARCHER, R. M., M.A., M.B. Camb., D.O.M.S.: surgical registrar, North Cambridgeshire Hospital, Wisbech.

HARRISON, G. K., M.A., M.D. Toronto, F.R.C.S.: chest surgeon, St. Thomas's Hospital, London.

JOCKEL, D. P. K., M.D. Glasg.: appointed factory doctor, Rotherham district, Yorkshire.

ROOKE, C. J., M.B. Camb.: appointed factory doctor, Plymstock district, Devon.

SMYTH, D. A., M.D. Durh., D.P.H.: asst. M.O., Worcestershire County Council.

SMYTH, W. B. A., M.B. St. And., D.P.H.: deputy M.O.H. and school M.O., Swindon.

TAYLOR, A. R., M.A., M.B. Aberd., F.R.C.S.E.: consultant neurosurgeon, Royal Victoria Hospital, Belfast.

TOWSON, R. T., B.A., M.D. Dubl.: asst. chest physician (S.H.M.O.), Leeds chest clinic.

TYRRELL, J. H., M.B. Dubl., D.A.: asst. anæsthetist (S.H.M.O.), Pontefract and Castleford H.M.C.

Manchester Regional Hospital Board:

BIRD, C. A. K., M.R.C.S.: consultant group pathologist, Macclesfield and Parkside Hospitals.

DALY, R. A., M.SC. Dubl., L.R.C.P.I.: consultant group pathologist, Rochdale hospital centre.

ROBSON, W. A., M.B. Manc., M.R.C.O.G.: asst. consultant obstetrician/gynæcologist, Preston and Chorley hospital centre.

North-East Metropolitan Regional Hospital Board:

DIGNAN, J. F., M.B. Dubl., F.R.C.S.I., D.PHYS.MED.: part-time consultant physician in physical medicine, North Middlesex Hospital and annexes.

HALL, I. M., M.D. Lond., M.R.C.P.: part-time consultant physician, Tilbury and Riverside Hospitals.

MORRISON, C. J. R., L.R.C.P.E., D.M.R.D.: part-time consultant radiologist, Mildmay Mission, Plaistow and Claybury Hospitals.

PALMER, K. W. N., L.M.S.S.A., D.PHYS.MED.: part-time consultant physician in physical medicine, St. Mary's Hospital, Colchester, and other hospitals in the group.

ROBINSON, M. I., M.B. Belf., D.M.R.D.: part-time consultant radiologist, Forest Hospital.

SEFTON, LOUIS, M.R.C.P.: part-time consultant dermatologist, Prince of Wales's General Hospital.

South-West Metropolitan Regional Hospital Board:

BARTLETT, DENIS, M.B. Lond., F.R.C.S.: consultant E.N.T. surgeon, Farnham group of hospitals.

DOBSON, S. C., B.M. Oxfd: consultant pathologist, Southampton group of hospitals.

MACHELL, E. S., M.B. Sheff., D.A.: consultant anæsthetist, board's western thoracic unit.

MELLOR, E., M.D. Manc.: asst. psychiatrist, St. James's Hospital, Portsmouth.

STEWART, G. T., M.D., B.SC. Glasg., D.T.M.&H.: consultant pathologist, Croydon group of hospitals.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally

Obituary

MILSOM REES

G.C.V.O., D.Sc., F.R.C.S.E.

Sir Milsom Rees, who was for many years laryngologist to King George V and to Queen Mary, died at his home at Broadstairs on April 23.

He was born at Neath, Glamorgan, in 1866, and he received his medical education at St. Bartholomew's Hospital, London, where he qualified in 1889. He was early attracted to laryngology, and after holding a resident appointment at the Hospital for Diseases of the Throat, Golden Square, he took the Edinburgh fellowship in 1892 and settled in consultant practice. In due course he joined the staffs of the Prince of Wales's General Hospital, Tottenham, and of the Sussex Throat and Ear Hospital, Brighton. The management of the singing and speaking voice was the part of his specialty that he made pre-eminently his own, and he was laryngologist to the Royal Opera House, Covent Garden, and to the Guildhall School of Music. Apart from his service to these institutions, he numbered among his patients and friends Madam Patti, Dame Nellie Melba, and many other famous singers.

Besides his appointment to the King and Queen he was also laryngologist to the late Queen Alexandra and to the late Queen Maude of Norway, and his services to the Royal House were recognised by his appointment as C.V.O. in 1911, and his promotion to K.C.V.O. in 1923 and to G.C.V.O. in 1934. He was also created a knight bachelor in 1916.

Outside his profession he had many business interests which often took him to Africa, and he did not neglect the wider opportunities for medical service which they offered him. In 1925, at the request of the government of the Sudan, he was called in to operate on Sir Sayed Ali in Khartoum. Later, at Sir Milsom's suggestion, and with his generous coöperation, a hospital was built at Arusha in Tanganyika near his coffee estates. Always an all-round athlete—at school and at hospital he had played cricket and football and boxed—he took part in big-game investigations in Central Africa, Tanganyika, Kenya, and Madagascar; and he also proved himself a good shot. He was for many years a keen golfer.

In London he served on the committees of many hospitals. To those with which he was closely associated he gave much practical help, and at St. Bartholomew's Hospital an operating-theatre bears his name. He was also interested in education, and in 1933 he established two scholarships at a preparatory school for the sons of medical men. Of late years he had to contend with the after-effects of a severe accident, and he spent most of his time at his home in Broadstairs.

He married in 1894 Miss Eleanor Jones, of Finchley.

DAVID WALLACE

K.B.E., C.M.G., LL.D., M.B. Edin., F.R.C.S.E., D.L.

Sir David Wallace, the doyen of Edinburgh surgeons, died in his 90th year at his home in Edinburgh on April 21. Over a long period he was one of the leading consultant surgeons of the city, and he had given particular attention to the development of urological surgery.

A Fifer, he was born at Balgrummo and educated at Dollar Academy and the University of Edinburgh. He graduated M.B. in 1884 and he obtained the F.R.C.S.E. three years later. When the South African war broke out he had already been appointed to the staff of the Edinburgh Royal Infirmary and had published a substantial body of work on genito-urinary surgery, especially cystoscopy. He was also lecturer on surgery at Surgeons' Hall. But he interrupted his career to serve in South Africa where he took charge of the Edinburgh South African Hospital.

On his return to Edinburgh he took up the threads of his consultant practice, and in due course he was promoted full surgeon at the Royal Infirmary. Later he became lecturer in clinical surgery at the university. His war-time experience had impressed him with the importance of the British Red Cross Society; he became honorary secretary of the Edinburgh branch when it was tarted in 1908, and in 1923 he was elected chairman. During the 1914–18 war he was appointed C.M.G., and at its close he was created K.B.E., and made a deputy-ieutenant of the City of Edinburgh. In 1930 the university conferred on him the honorary degree of LL.D.

In retirement he remained physically and mentally alert and he continued to work on hospital organisation. He outlived most of his contemporaries, but his many activities brought him into contact with people in all walks of life who will mourn the loss of a friend and helper.

In 1905 Sir David married Miss Augusta Maud Clouston, a daughter of the late Sir Thomas Clouston, M.D. She survives him with two sons.

RICHARD HOWARD MOLE

B.A. Lond., M.D. Lpool

Dr. R. Howard Mole died on April 10 in his 76th year. He was educated at Kingswood School, at Aberystwyth University College, where he graduated in arts in 1897, and at Liverpool University, where he took his M.B. with honours in 1905. As a house-surgeon at the Liverpool Royal Infirmary, he watched Paul experiment with the use of rubber gloves for operations—only to discard them later. He was successively Holt fellow in physiology (under Sherrington) and Holt fellow in pathology. In 1906 he proceeded to his M.D. degree, and soon afterwards he was appointed pathologist at the Royal Southern Hospital at Liverpool.

In 1911, with Arthur Jackson, he sailed for China to join the staff of the newly founded Moukden Medical College in Manchuria. Jackson died of bubonic plague a few weeks after they arrived, but the tragic example of his sacrifice did much to help the work of the college, which became one of the foremost teaching schools in China. Dr. Mole taught preclinical subjects, founded anatomy and pathology departments, and was a surgeon to the hospital for 18 years. As a teacher he had unusual difficulties to surmount. For instance, he had to invent a Chinese vocabulary in anatomy. Again, from time to time when the local authorities were hostile, parts for dissection were unobtainable, and Dr. Mole had to bring specimens in his personal baggage from England. In 1926 he attended Marshal Chang-tso-lin at the time of his assassination by the Japanese, the event which set the stage for the Manchurian Incident and the subsequent Sino-Japanese War.

In 1929 Mole returned to Liverpool to become once more pathologist to the Royal Southern Hospital, the post he had left nearly twenty years before, and took charge of the same laboratory rooms. The new laboratory block which he designed had not been long in use before the hospital had to be evacuated from the dock area because of bombing. On reaching the age-limit he retired from the hospital, but he continued work as pathologist to the Birkenhead and Wirral Children's Hospital and other hospitals until last summer. He had four sons; one is a pathologist, one a medical student, and two were killed in the war.

DR. R. W. DODGSON

A FRIEND who had official contacts with Dr. Dodgson at the Ministry of Agriculture and Fisheries writes:

"What seemed specially to distinguish his work on shellfish purification was his biological approach to the pollution problem in mussels and oysters no less than to the problems of oyster-breeding, the fierceness of his scientific integrity and standards, his absolute devotion to the work which he set himself to do. Bacteriologically he was pre-eminently equipped for studying shellfish pollution and its dangers to the public health; but his method of achieving safety by purification in sterile water was based on the most careful physiological study of the mussel itself, and he was not satisfied merely to adopt standards of purity. He urged constantly that the danger of pollution must be assessed by topographical study of the mussel beds, and under all conditions of tides and wind.

"To him universal cleansing of shellfish was a crusade and one in which only the most trusted and proved weapons must be used. He had a contempt for ex-cathedra pronouncements and was no respecter of persons. His position was one of delicacy, for the closing of shellfish beds was the duty of another authority; but it was for him to show through his own department how the fishery could be kept open for the benefit of those who earned their living from it without danger to the public health.

"Most notable though his achievements were in the field in which he chose to work for so many years, his gifts and ability were such that one wished at times that they could have been used in attacking some of the even greater ills of mankind. From this he would, no doubt, have dissented vehemently. Resolute in controversy and in the exposure of a too confident adversary, and with a humorous and mildly cynical view of potentates, he was a gentle and thoughtful friend, with no care for himself."

PROF. G. B. FLEMING

A. M. writes: "Geoffrey Fleming took over presidency of the British Pædiatric Association after the war and was most successful in the chair at the first post-war meeting. He followed Leonard Parsons, who had held office for four years, and despite many difficulties Fleming carried out his task with great skill, kindness, and charm. He continued to be a most valuable "elder statesman" to whom one naturally turned for advice, and the result was always sound and helpful. He was, as others have written, a charming host. Perhaps it is significant that a picture of a favourite horse had a prominent place in his living-room in his lovely home in Glasgow, and he kept up his hunting as long as it was possible. He loved those aspects of country life which could be maintained from a base in town. He equally enjoyed his club and meeting his many friends—not all members of the medical profession. This varied background gave Fleming a poise and a wisdom which was the envy of his younger colleagues. Such envy was, however, essentially benevolent because Fleming inspired benevolence. He was, to use a phrase too often debased, a sweet person. He combined an almost childlike enjoyment of life with a maturity of outlook which influenced all who came in contact with him."

[Annan

W. W. G. writes: "I first knew Professor Fleming in my student days when he taught in the wards of the Western Infirmary. Later I was his junior colleague on the staff of the Royal Hospital for Sick Children, and for the past decade I had the privilege of working in the closest coöperation with him on the council of the Royal Faculty of Physicians and Surgeons and throughout his tenure of office as president of that ancient corporation.

"Professor Fleming belonged to one of the oldest Glasgow families; he was a Burgess of the City as had been his forebears through fourteen generations in direct line. He was a man of the highest principles, and as he had ample private means he did not consider it right to accept payment for any services, and indeed he made large contributions to every good cause. To the Royal Faculty he was always a generous benefactor, and only a few days before his death he presented to it a notable portrait of its founder, King James VI of Scotland and I of England. He also gave a large sum of money to inaugurate a fund for postgraduate medical education. The Royal Faculty has been blessed by many outstanding men who have occupied its presidential chair and Fleming must be regarded as among the greatest of these. His counsel and judgement were of inestimable value and he was ever ready to give his time without stint. He became the ideal elder statesman and his passing is a grievous blow which will be felt in Glasgow and the West of Scotland. His name will live in the annals of the Royal Faculty of Physicians and Surgeons."

Notes and News

FAMILY ALLOWANCES AND NATIONAL INSURANCE BILL, 1952

OVER 3 million family allowances and nearly 6 million insurance pensions and benefits will be increased by the end of September if this Bill,[1] which was published on April 24, is passed by Parliament. The changes in allowances, benefits, and pensions to be made under the Bill are:

FAMILY ALLOWANCES

The present allowance of 5s. a week for each child in the family after the first will be increased to 8s.

NATIONAL INSURANCE

The basic weekly rate of *unemployment and sickness benefit* will be increased from 26s. for a single person and 42s. for a married couple to 32s. 6d. and 54s. respectively.

The distinction will be abolished between the basic rate of *retirement pension* for those who reached pensionable age before Oct. 1, 1951 (30s. for a single person, 50s. for a married couple) and for those who reached it after that date (26s. for a single person, 42s. for a married couple). More than 4 million retirement pensioners will receive the new basic rate of 32s. 6d. for a single person and 54s. for a married couple.

Widow's pension will be increased from 26s. to 32s. 6d. a week, *widowed mother's allowance* (including provision for one child) from 40s. to 43s., and *guardian's allowance* from 13s. 6d. to 16s. a week.

INDUSTRIAL INJURIES

Injury benefit will be increased from 45s. to 55s. a week for a single person and from 61s. to 76s. 6d. a week for a married couple. The 100% *disablement pension* will also be increased from 45s. to 55s. a week with proportionate increases for lower assessments and in the gratuities for assessments below 20%. *Pensions for widows* at present payable at 30s. will be increased to 37s. a week.

The following increases of weekly contributions will be paid from next October (present rates in parentheses):

	Men	Women
Employed Persons		
Paid by employed person	5s. 9d. (5s. 1d.)	4s. 6d. (4s.)
Paid by Employer ..	5s. 0d. (4s. 4d.)	3s. 11d. (3s. 5d.)
Total ..	10s. 9d. (9s. 5d.)	8s. 5d. (7s. 5d.)

The above rates include Industrial Injuries contributions.

	Men	Women
Self-employed Persons	7s. 5d. (6s. 6d.)	6s. 2d. (5s. 5s.)
Non-employed Persons	5s. 7d. (5s. 0d.)	4s. 5d. (4s.)

The additional cost to the Exchequer of the increase in family allowances will be about £23 million in the current financial year and £30 million in 1953-54, but there will be a consequent decrease in National Assistance payments of just over £1 million. The new contribution rates, with the proportionately higher Exchequer supplement, will increase the income of the Industrial Injuries Fund by about £3,400,000, and the initial additional cost of the higher benefits will be about £3,500,000. The additional income to the National Insurance Fund from the higher contributions and the Exchequer supplement will be £33 million in the present financial year and £60 million in 1953-54. The additional cost of the higher benefits will be £32 million in the present financial year and £59 million in 1953-54. The extra income to the Fund will remain fairly constant over the next twenty-five years; but the extra expenditure, while slightly below the income in the first few years, will then increase rapidly to exceed the income by £36 million in 1977-78. The first general review of the scheme will be made in two or three years' time, and the Government actuary believes that it will then be necessary within a short period to consider further financial provision.

As a result of the increases in insurance benefits there will be a decrease of about £11 million in National Assistance payments.

APPLIED STATISTICS

THE Royal Statistical Society already publishes its own journal, but the council of the society knew that a publication entirely devoted to the working-out of statistical methods in practice was also in demand, and they have accordingly founded one. As Prof. A. Bradford Hill, the president, remarks in a foreword to the first number, for every person interested in theoretical statistics there are many who are more closely concerned with the application of the new methods, and it is to them that *Applied Statistics* is addressed. Its aim is to help all workers concerned with statistics in industry, commerce, science, and the many other branches of modern life where statistical methods can profitably be applied. By making the value of such methods in raising efficiency more widely appreciated, the journal will give a stimulus to production in many divisions of industry.

The first number appeared last month and included an article on the introduction of statistical methods to industry, a statistician's view of the International Management Congress of 1951, and an account of how to estimate the social class of large towns—an index helpful to economists and not easy to determine directly.

The annual subscription is 25s., and the journal is to be published three times a year by Messrs. Oliver & Boyd Ltd., Tweeddale Court, Edinburgh 1.

EXTRAVAGANT PRESCRIBING

WHEN the large numbers of National Health Service prescriptions made it impossible for the pricing bureaux to cope with the investigation of excessive prescribing, the Minister of Health set up a central investigation unit to detect and report extravagances. From March, 1950, to November, 1951, 277 practitioners were thought to have prescribed wastefully; this figure is given by the Comptroller and Auditor-General in a report which prefaces the summarised accounts of the National Health Service for 1950-51.[1] Most of these doctors were visited by the Ministry's regional medical officers, and warning letters were sent to over half of them. Several doctors continued to prescribe in a way that seemed excessive, and the facts have been reported to the local medical committees, whose statutory duty it is to consider such cases when they are brought to their notice by the Minister. Should a committee decide that the cost exceeds a reasonable estimate for all proper treatment, the Minister may direct that some of the cost be recovered from the doctor.

RHEUMATOID ARTHRITIS AND TRAUMA

THAT trauma sometimes determines the onset of rheumatoid arthritis is indicated by Edström[2] in an account of 2034 cases of this disease, in 72 (3·5%) of which trauma had precipitated the onset. The trauma consisted of acute mechanical injury in 59 cases, acute thermal injury in 8 cases, and physical strain in 5 cases. In all 72 cases the injured joint was the first affected; and in 4 the process remained confined to the one joint. (Edström makes it clear that only cases of true rheumatoid arthritis are included in his series.) The 72 patients comprised 57 men and 15 women, whereas men accounted for only a third of the whole series of 2034; and Edström suggests that the reason for this difference is that men are more often exposed to trauma.

CODE OF SURGICAL OPERATIONS

LAST year the General Register Office issued parts 1 and 2 of a code of surgical operations. The first appendix—a classification of radiotherapy procedures—has now been issued.

University of Glasgow

On April 26, the degree of M.D. was conferred on the following:

J. H. Bell, Mabel E. Mitchell, Mary D. Smith (with high commendation); *R. M. Gibson (with commendation)*

University of Birmingham

On April 21 Prof. A. P. Thomson unveiled a bronze bust of Dame Hilda Lloyd which has been presented to her in recognition of the honour she has brought the school in becoming the first woman president of the Royal College of Obstetricians and Gynæcologists and the second president from Birmingham. The bust, which is to stand in the entrance of the medical school, is by Mr. Jacob Epstein.

A Hospital Renamed

By permission of the Queen the name of the Glasgow Royal Cancer Hospital and Glasgow and West of Scotland Radium Institute has been changed to the Royal Beatson Memorial Hospital. The new name was chosen in honour of the late Sir George Beatson, M.D., who was largely responsible for the establishment of the hospital and its research department.

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[1] Cmd. 8517. H.M. Stationery Office. 3d.

[1] Summarised Accounts of Regional Hospital Boards, Boards of Governors of Teaching Hospitals, Hospital Management Committees, Executive Councils, and the Dental Estimates Board for England and Wales for the Year ending March 31, 1951. H.M. Stationery Office. Pp. 39. 2s.

[2] Edström, G. *Acta med. scand.* 1952, 142, 11

yal College of Physicians of London

At a comitia held on April 24, with Sir Russell Brain, the sident, in the chair, the following members were elected the fellowship:

R. H. QUENTIN-BAXTER, Christchurch, N.Z.; H. W. WUNDERLY, nberra; F. C. O. VALENTINE, London; I. M. ALLEN, Wellington, Z.; DORIS BAKER, London; C. C. CHESTERMAN, London; J. R. AZÉ, Colombo; A. S. HALL, Aylesbury; VICTORIA SMALLPEICE, ford; P. B. FERNANDO, Colombo; R. W. LUXTON, Manchester; L. HOFFMAN, Bath; N. F. MACLAGAN, London; Lieut.-Colonel ER MUHAMED KHAN MALLICK, Lahore; T. A. LLOYD-DAVIES, ttingham; E. G. BREWIS, Newcastle upon Tyne; T. E. LOWE, lbourne; T. N. FRASER, Glasgow; Hon. W. S. MACLAY, London; H. J. MAXWELL TELLING, Leeds; D. M. T. GAIRDNER, Camdge; MICHAEL GELFAND, Salisbury, Rhodesia; D. A. K. BLACK, nchester; G. A. SMART, Newcastle upon Tyne; ISAAC MUENDE, ndon; R. C. MAC KEITH, London; H. A. BURT, London; R. A. J. HER, London; FRANCES V. GARDNER, London; A. C. FRAZER, rmingham; D. W. SMITHERS, London; K. W. DONALD, Birmingm; A. H. T. ROBB-SMITH, Oxford; Air Commodore C. A. MBALL, London.

The following were elected to the fellowship under by-law b, which provides for the election of non-members "who ve distinguished themselves in any branch of the service or actice of medicine.":

ALI BEDRI, Khartoum; Sir RUDOLPH PETERS, F.R.S., Oxford.

Conway Evans prizes were presented to Sir Gordon Holmes, R.S., for his contribution to British neurology, and to rof. S. P. BEDSON, F.R.S., for his researches into the bacteriogy of viruses.

The following, having satisfied the censors' board, were ected to the membership:

Harry Altman, M.B. Witw'rsrand; G. C. Arneil, M.D. Glasg.; J. Bailey, M.B. Cape Town; C. H. Baird, M.B. N.Z.; Sunder xman Balse, M.B. Bombay; P. J. Banks, M.B. Lond.; J. B. erry, L.R.C.P.; D. A. Brewerton, M.D. McGill; G. H. Choa, B. Hong-Kong; K. M. Citron, M.D. Lond.; Owen Clarke, D. Camb. W. I. Cranston, M.B. Aberd., squadron-leader, R.A.F.; H. Diggle, M.B. Manc.; C. O. Edwards, M.B. Camb.; R. W. manuel, B.M. Oxfd; Joseph Erulkar, M.B. Durh.; R. J. Fassina, D. Queen's Univ., Ontario; H. D. Friedberg, M.B. Witw'rsrand; aurice Garretts, M.B. Lond.; Leonard Haas, M.B. Camb.; Philip aden, M.B. Camb.; G. V. Hall, M.B. Sydney; Frank Hawking, M. Oxfd; I. G. W. Hill, M.D. Edin.; Michael Honey, M.B. Camb.; R. Horler, M.B. Durh.; M. S. Israel, M.B. Witw'rsrand; D. A. cGreal, M.B. St. And.; C. J. McRae, M.B. Melb.; W. E. Medd, B. Lond.; M. O. R. Medonza, L.M.S. Ceylon; R. A. Melick, B. Sydney; M. J. D. Newman, M.B. Camb.; R. M. Norman, D. Bristol; W. E. Parkes, M.D. Belf.; W. M. O. Purcell, M.D. U.I.; H. H. Ronn, M.B. Lond., surgeon lieutenant, R.N.; J. C. A. ibley, M.D. Queen's Univ., Ontario; E. S. Snell, M.B. Lond.; K. L. tuart, M.B. Belf.; J. R. Sudbury, B.M. Oxfd, flying-officer, R.A.F.; L. V. Summerhayes, M.B. Lond.; Noshir Hormusji Wadia, D. Bombay; D. C. Wallace, M.B. Sydney; Margaret E. H. T. Varwick, B.M. Oxfd.

Licences to practise were conferred upon the following 149 andidates (116 men and 33 women) who have passed the inal examination of the conjoint board:

D. A. Andrews, L. G. Andrews, A. P. C. Bacon, K. D. Bagshawe, V. Balmforth, P. J. Barclay, N. H. Barley, D. N. Bates, D. H. ayton, C. L. Belcourt, L. A. W. Bellamy, R. A. Bennett, Hilary A. erry, Phyllis E. Billinge, E. W. G. Birch, G. W. Bisset, Joy S. light, Gisela Boss, R. W. Brotherwood, G. L. Brown, C. J. uckingham, Winifred Burgess, L. J. Burns, J. D. K. Burton, R. Carmichael, Sylvia J. Clapp, R. H. Clark, D. L. Clarke, H. L. larke, Heather R. Clay, T. S. Cookson, Mary Crawford, Daphne I. L. DaCosta, R. H. Davison, John Dennis, J. S. Dodge, D. R. Dodsley, W. A. C. Dow, Marie G. Drew, R. M. L. Dry, Sylvia I. Duckworth, H. P. Duke, John Eastwood, D. W. Ebrahim, P. S. Elias, F. C. Emberton, L. L. Emery, John Ernsting, R. S. K. Essame, Jean M. Evans, R. R. Evans, C. A. Ezike, I. R. Ferdinand, Elizabeth Fincham, R. F. Fisher, D. J. Flight, Eva A. Frommer, J. R. G. George, N. P. H. Gibbs, P. R. Gilbert, Hilary B. Gostling, D. K. Gray, D. F. Hadman, M. C. Hall, Thomas Hall, D. C. Harris, E. G. Haydon, N. St. J. Hennessy, Laurence Henry, J. H. Highman, N. A. Hiley, Arthur Honey, D. O. Hughes, F. C. Hurrell, J. R. F. Ingall, B. G. Jackson, Emily B. John, Thelma D. Johnson, T. G. R. Jones, Wendy Jones, R. C. Jordan, G. M. S. Keogh, Sylvia L. Kingsbury, R. M. Kirk, Daphne M. Kirkman, P. D. Lamb, J. A. Lewis, S. D. Libbert, C. A. Linsell, Betty Llewelyn, J. F. Lowe, K. R. Lown, Margaret Luing, David McQueen, Marcel Malden, B. L. Mallett, C. R. A. Martin, W. A. Matheson, A. H. Maynard, B. G. Mendelsohn, T. W. Merrick, T. R. Mogila-Stankiewicz, K. S. Mooleedhar, Rosemary A. Morrell, I. G. Mowat, Hamish Nichol, Joyce B. Nunneley, Gillian Oliver, R. M. Oliver, C. H. Opie, Mary C. Peard, . F. Peeks, N. T. Pollitt, E. C. V. Price, Aftaboor Rahman, D. A. ands, J. D. Ross, N. J. W. Royston, Imrich Sarkany, Vishnu arma, S. W. Scargill, Aboudy Selim Shamash, G. B. Skinner, L. Skinner, J. G. Slater, A. J. Smith, M. C. Solomon, Anthony pellman, Margaret A. E. Stuart, H. A. J. Thomas, H. L. Thomas, atricia M. Thompson, H. H. Thomson, O. R. Todd, Molly E. owell, Maung Tun Shwe, Barbara V. Tyman, Margaret I. Upton, rudence Valentine, C. H. Vigar, P. O. Wakelin, Joanna M. Ward, H. W. Warne, G. F. Whyntie, H. J. W. Willson, R. E. Wolfendale, A. Woodbridge, E. G. B. Worthington, F. A. Yates.

The following diplomas and those mentioned in our issue of pril 12 (p. 773) were conferred jointly with the Royal College f Surgeons:

D.O.—L. I. Phillips.
D.A.—A. E. Hocking, W. N. Wild.
D.T.M.&H.—Brian Devlin, Asoke Kumar Mitra, D. M. Montgomery.

Dr. E. B. Strauss will deliver the Croonian lectures on Tuesday and Thursday, May 6 and 8, at 5 P.M., at the college, Pall Mall East, London, S.W.1. He is to speak on Reason and Unreason in Psychological Medicine.

Guy's Hospital, London

Dr. Alfred Blalock will deliver the Carbutt lecture on Monday, May 19, at 5 P.M. at the hospital, London Bridge, S.E.1. He is to speak on Cardiovascular Surgery.

Congress on Military Medicine

The 15th congress of the Office International de Documentation de Médecine militaire will be held at Liége and Brussels from June 4 to 7. Further particulars may be had from Colonel-Médecin Tonglet, 511, avenue Louise, Brussels, Belgium.

International Conference on the Home Help Service

The first International Conference on the Home Help Service will be held under the auspices of the National Association of Home Help Organisers, on May 7, 8, and 9, at the Abbey Community Centre, 29, Marsham Street, Westminster, S.W.1. Representatives from European and Scandinavian countries and from the United States will exchange views and methods of information. Further particulars may be had from the honorary public relations correspondent of the association, 31, Margaretta Terrace, S.W.3.

Royal Statistical Society

The study section of this society has formed a study circle to examine statistical problems in medicine. Meetings, at which informal papers are read and discussed, are held monthly and are open to all who are interested. The next meeting will be held at 6 P.M. on May 27 at the Westminster Medical School, Horseferry Road, London, S.W.1, when Mr. J. A. Heady will discuss the work of the Medical Research Council social medicine research unit. Further information may be obtained from Miss M. Landreth, Gordon Hospital, Vauxhall Bridge Road, S.W.1.

Royal Appointments

The following have been appointed honorary physicians to the Queen:

Samuel Barron, M.R.C.P.I., M.O.H. Belfast.
Walter Eric Chiesman, F.R.C.P., medical adviser to Her Majesty's Treasury.
Sydney Walter Fisher, M.D., principal medical inspector, Mines Department, Ministry of Fuel and Power.
Arthur Massey, C.B.E., M.D., chief medical officer, Ministry of National Insurance.
Robert Hughes Parry, F.R.C.P., M.O.H. Bristol, and professor of preventive medicine, University of Bristol.
Harry James Rae, M.C., M.B., M.O.H. Aberdeen.

The appointments are until June 30, 1953.

Institute of Hospital Administrators

In celebration of its 50th anniversary, the institute is holding a jubilee conference in London at the Caxton Hall, S.W.1, on May 8, 9, and 10. Mr. H. F. C. Crookshank, the Minister of Health, will open the conference; and other speakers will include Mr. J. E. Pater, under-secretary, Ministry of Health, who will read a paper on the Rôle of the Central Department in the Hospital Service; Mr. V. W. Grosvenor, LL.B., chairman of the Birmingham Regional Hospital Board (the Regional Organisation of Services); Mr. F. S. Stancliffe, chairman of the Association of Hospital Management Committees (the Hospital Management Committee and its Administration); and Mr. Richard Titmuss, professor of social administration in the University of London (the Hospital and its Patients).

Tuberculosis Conference

The third Commonwealth and Empire Health and Tuberculosis Conference is to be held in London from July 8 to 13. The speakers will include Dr. I. L. Briggs (Northern Rhodesia), Dr. G. C. Brink (Department of Health, Ontario, Canada), Dr. V. Clausen (Vordingborg Sanatorium, Denmark), Miss E. Cockayne (chief nursing officer, Ministry of Health), Dr. F. van Deinse (chief, B.C.G. department, Institut Pasteur, Paris), Dr. P. W. Dill-Russell (Nyasaland), Dr. Charles Hill, M.P., Dr. J. B. McDougall (World Health Organisation), Dame Dehra Parker (minister of health, Northern Ireland), and Dr. J. A. Scott (M.O.H., County of London). Further information may be had from the N.A.P.T., Tavistock House North, Tavistock Square, London, W.C.1.

General Board of Control for Scotland

Sir Garnet Douglas Wilson, LL.D., J.P., a former lord provost of Dundee, has been appointed an unpaid commissioner of the board.

International Scientific Film Association

The International Scientific Film Association are to hold their congress this year in Paris from Sept. 23 to Oct. 1.

Howard League for Penal Reform

At a meeting of this society at the Alliance Hall, Palmer Street, London, S.W.1, on Monday, May 12, at 6.30 P.M., Mr. Glanville Williams, Quain professor of jurisprudence in the University of London, will speak on the Reform of the Criminal Law.

Rockefeller Foundation

The foundation has made a grant of $200,000 to the Karolinska Institute in Stockholm to set up an experimental surgical laboratory under the direction of Prof. Clarence Crafoord. The laboratory is to serve as a training centre for European surgeons specialising in circulatory and respiratory disorders.

The foundation has also given $105,000 to the Tavistock Institute of Human Relations, London, for their research into group and community behaviour.

EMERGENCY BED SERVICE.—In the week ended last Monday applications for general acute cases numbered 970. The proportion admitted was 88·8%.

Dr. W. J. O'Donovan has been made a knight of the Papal Order of St. Gregory the Great.

Prof. R. J. S. McDowall is to lecture in Florence and Leiden during the first week in May.

Sir Andrew Davidson, at the invitation of the World Health Organisation, is to lead a group of senior public-health administrators *from 18 European nations who are visiting Norway and France this summer. For this purpose Sir Andrew has been appointed a consultant to W.H.O.*

A British standard for bed strippers for use in hospitals has been issued [illegible] bed stripper is to provide [illegible] othes stripped from a bed [illegible] rd are obtainable (2*s*. eac [illegible] Sales Branch, *24, Victoria Street, London, S.W.1.*

Births, Marriages, and Deaths

BIRTHS

CALNAN.—On April 24, at Oxford, the wife of Mr. James Calnan, F.R.C.S., M.R.C.P.—a daughter.
COWAN.—On April 18, in London, the wife of Dr. Allan Cowan —a son.
EARLE.—On April 17, the wife of Dr. J. E. G. Earle, of Elmham, Norfolk—a daughter.
FALKNER.—On April 18, in London, the wife of Dr. Frank Falkner —a daughter.
MACINTOSH.—On April 20, at Aberdeen, the wife of Dr. Alistair Macintosh—a son.

MARRIAGES

GRIBBLE—WATKINS.—On April 19, in Dulwich, Michael de Gruchy Gribble, B.M., to Patricia Mary Watkins.
HEPWORTH—MACLEAN.—On April 23, at Mirfield, Richard Gordon Hepworth, M.R.C.S., to Sheina Audrey MacLean, M.B.
NICOLSON—FORBES.—On April 18, in Edinburgh, Edward Lawford Nicolson, F.R.C.S.E., to Elizabeth Forbes.
REYNOLDS—WICKS.—On April 26, in London, David Farmer Reynolds, M.B., to Betty Theodora Wicks, M.SC.

DEATHS

LACE.—On April 22, Frederick Lace, F.R.C.S., of Bath, aged 88.
MARSHALL.—On April 23, at Bideford, Devon, Arthur Thomson [illegible]
[illegible] chard Howard Mole, B.A., M.D. Lpool, of [illegible] and of Moukden Medical College, China.
[illegible] April 24, at Bath, Henry Norman-Barnett, [illegible], R.A.M.C.
[illegible] roadstairs, Sir Milsom Rees, G.C.V.O., D.SC., F.R.C.S.E., aged 86.
ROBERTS.—On April 25, at West Worthing, Frederick Emilius Roberts, D.S.O., O.B.E., M.R.C.S., D.P.H., lieut.-colonel, R.A.M.C. retd, aged 73.
SHARRARD.—On April 25, in London, Ethel Margaret Sharrard, M.B. Sheff., aged 35.
TAYLOR.—On April 24, at Hailsham, Thomas Sigston Taylor, B.CHIR. Camb.
WALLACE.—On April 21, in Edinburgh, Sir David Wallace, K.B.E., C.M.G., D.L., M.B. Edin., F.R.C.S.E., aged 89.
WOODRUFF.—On April 23, Charles Reynolds Woodruff, M.B.E., M.R.C.S., of Bentinck Street, London, W.1.

Diary of the Week

MAY 4 TO 10

Monday, 5th

LONDON SCHOOL OF HYGIENE, Gower Street, W.C.1
5.30 P.M. Dr. A. Lwoff (Paris): Development at the Cell Level—Self Reproducing Particle in the Developmen Ciliates. (First of three lectures.)

ROYAL EYE HOSPITAL, St. George's Circus, S.E.1
5 P.M. Dr. T. H. Whittington: Care and Treatment of Myopic Patient.

UNIVERSIT[illegible]
5 P.M. [illegible] Edinburgh.) Dr. Franci M[illegible] Response to Surgery. (F of three lectures.)

Tuesday, 6th

ROYAL COLLEGE OF PHYSICIANS, Pall Mall East, S.W.1
5 P.M. Dr. E. B. Strauss: Reason and Unreason in Psy logical Medicine. (First of two Croonian lectures.)

LONDON SCHOOL OF HYGIENE
5.30 P.M. Dr. Lwoff: Development at the Cellular Level— Cycle of Bacteriophage in Lysogenic Bacteria. (Sec of three lectures.)

ROYAL EYE HOSPITAL
5 P.M. Prof. Arnold Sorsby: Genetics in Ophthalmology.

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hos Medical School, W.2
5 P.M. Prof. G. R. Cameron, F.R.S.: Pathology at the Crossro (Almroth Wright lecture.)

UNIVERSITY OF EDINBURGH
5 P.M. Dr. Moore: Surgical Metabolism and the Endoc Glands. (Second of three lectures.)

Wednesday, 7th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Section of History of Medicine.* Dr. Charles Sin A Peep into Anglo-Saxon Medicine.

ROYAL EYE HOSPITAL
5.30 P.M. Mr. L. H. Savin: Ptosis.

UNIVERSITY OF CAMBRIDGE
5 P.M. (Senate House, Cambridge.) Sir Russell Brain, P.R.C. Contribution of Medicine to Our Idea of the Mi

MANCHESTER MEDICAL SOCIETY
4.15 P.M. (University of Manchester.) Dame Hilda Llo F.R.C.O.G.: Twins.

INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Str W.C.2
5.30 P.M. Dr. J. O. Oliver: Hospital Infections.

[illegible] OF EDINBURGH
[illegible] f Surgeons, 18, Nicolson Str [illegible] Attempted Suicide.

UNIVERSITY OF EDINBURGH
5 P.M. Dr. Moore: Study of Body Composition by Isot Dilution. (Last of three lectures.)

Thursday, 8th

ROYAL COLLEGE OF PHYSICIANS
5 P.M. Dr. Strauss: Reason and Unreason in Psycholog Medicine. (Second of two Croonian lectures.)

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
3.45 P.M. Prof. R. J. Last: Pectoral Girdle. (Arnott dem stration.
5 P.M. Mr. William Gissane: Surgery of Accidents and Social Significance. (Joseph Henry lecture.)

ST. *GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Cor* S.W.1
5 P.M. Sir Paul Mallinson: Psychiatry lecture-demonstratio

WEST END HOSPITAL FOR NERVOUS DISEASES
5.30 P.M. (Department of Psychiatry, 48, Cosway Street, N.W Dr. Colin Edwards: Functional or Organic Differe Diagnosis.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. C. W. McKenny: X-ray Technique.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
11 A.M. (Queen Charlotte's Maternity Hospital, Goldh Road, W.6.) Dr. H. K. Waller: Breast-feeding.

LONDON SCHOOL OF HYGIENE
5.30 P.M. *Dr. Lwoff:* Development at the Cellular L —Induced Development of Viruses and *of Non-infec Particles. (Last of three lectures.)*

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, S
5 P.M. Prof. D. O. Hebb (McGill University): Diagno Personality in Primates.

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Edinburgh.) Mr. A. MacPherson: Treatment of Portal Hypertension.

UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Prof. G Pickering: *Benign and Malignant Hypertension.*

Friday, 9th

ROYAL EYE HOSPITAL
4.30 P.M. Mr. A. J. Cameron: Plastic Operations and O Surgery.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. E. M. Wigley: Eczema.

B.C.G. VACCINATION AND TUBERCULIN ALLERGY*

CARROLL E. PALMER
M.D., Ph.D. Minnesota
DIRECTOR, TUBERCULOSIS RESEARCH OFFICE, WORLD HEALTH ORGANISATION, COPENHAGEN

It is now nearly three decades since B.C.G. vaccination against tuberculosis was first tried, on a relatively small experimental scale, in human beings. It gained little general usage, however, until about five years ago. Mass-vaccination campaigns were then started in several areas, and B.C.G. is now being used to some extent in almost every country throughout the world.

Despite its present world-wide use, there are many who suspect that the value of B.C.G. as protection against tuberculosis has not been satisfactorily proved, and that far too little is known about the vaccine itself and its effects on human beings. The deficiencies in our knowledge have become inescapably apparent during the large-scale international B.C.G. campaigns; and it was recognition of this ignorance that led the World Health Organisation to establish a Tuberculosis Research Office in Copenhagen early in 1949. The primary purpose of that office is to learn more about immunisation against tuberculosis and especially about B.C.G. vaccination.

During the past two years extensive field investigations have been carried out, including the study of some 30,000 Danish school-children. In investigating B.C.G. vaccine we have studied variations in its preparation; different concentrations of living bacilli, dead bacilli, and mixtures of the two; the traumatic effects of prolonged storage, heat, and light; variations in the technique of intradermal injection; and many other problems. Most of our results have not yet been published. One reason for this is that they differ so much from what is generally accepted about B.C.G. that much of the work has had to be repeated; another is that many questions have been raised which need further clarification.

What I shall give here is not a story of laboratory research, but almost entirely an account of work on human beings in connection with B.C.G. vaccination programmes. Each separate study was carefully planned and supervised; a sufficiently large number of persons was studied to give stable and scientifically reliable results. The field personnel underwent intensive training and every effort was made to follow uniform procedures and to eliminate personal bias from the observations. This work has required the joint effort of many people and many groups, and in describing it I am acting only as their spokesman.

THE BACKGROUND

Let me begin by restating a few basic facts:

1. B.C.G. is a living vaccine, prepared from a special strain of bovine tubercle bacilli of attenuated virulence which, when injected into man or animals, produces tuberculin allergy but not progressive disease.
2. An infection with B.C.G. is believed to confer some protection against a later infection with virulent tubercle bacilli.
3. It is considered unnecessary—and probably undesirable—to give B.C.G. to persons who have already been infected with virulent bacilli.

To select those persons who have not had a tuberculous infection, and may therefore benefit from vaccination, the tuberculin test is customarily used: an allergic reaction to tuberculin indicates that infection with virulent tubercle bacilli has already occurred. The tuberculin test is also used to judge wheth has been "successful": tuberculin alle vaccination is taken as evidence that t person has been infected with B.C.G. and has degree of immunity. Thus tuberculin i indispensable part of B.C.G. vaccination w

The use of the tuberculin test has co regarded as a simple matter. The results was supposed, are either positive or negat reactors should be vaccinated; those whc positive reactors are protected, and thos negative should be revaccinated. But no is considerable disagreement, even among specialists, as to just what a positive or a n culin reaction really is. In fact, our kno incomplete that much of the effort of o been devoted to investigating this problem the interpretation of B.C.G.-induced allergy. therefore, will deal primarily with the s tuberculin allergy in relation to B.C.G. vaccination.

PRE-VACCINATION ALLERGY

First, let me describe the results generally obtain when a *single tuberculin test is used to select people for vaccination*. Fig. 1 summarises the reactions of several thousand unvaccinated persons to the Mantoux 10 T.U. test.† It will be seen that about 45% had reactions which measured less than 2 mm. in diameter; rather more than 10% had reactions of 2–3 mm.; and fewer than 1% had reactions of 6–8 mm. Above 8 mm. there is a progressive increase in frequency, with a peak at 16–18 mm.; but very few persons had reactions as large as 30 mm. in diameter.

This bimodal distribution suggests that the population tested contains two groups, one giving reactions centred at 0–1 mm., with a scattering of reactions up to 6–8 mm., and another centred at 16–18 mm., with a scattering of reactions in both directions. The very low frequency of reactions measuring about 6 mm. indicates a break at this point; and if one knew nothing about tuberculin reactions other than the frequency distribution as shown here, it would be natural to suppose that this is where some simple factor divides the population into two different groups. And in fact 6 generally been accepted by many workers as the

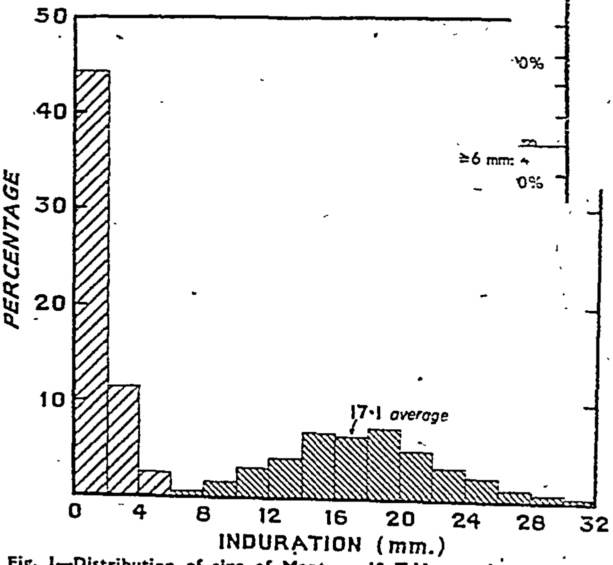

Fig. 1—Distribution of size of Mantoux 10 T.U. reactions: obtained before vaccination with B.C.G.

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* Given as the annual Malthe lecture of the Norwegian Medical Society, Oslo, on Nov. 14, 1951.

† 10 tuberculin units is equivalent to 0·0002 mg. o standard P.P.D. (purified protein derivative).

...ive and negative reactions, since most other evidence of tuberculosis show a ...east 6 mm. to the 10 T.U. Mantoux test.

POST-VACCINATION ALLERGY

...o the subject of tuberculin sensitivity ... vaccination, I shall present data from ...s: Denmark, Greece, and Egypt. The ...erial is from the intensive studies made ...ulosis Research Office, in coöperation with ...institut in Copenhagen and with the ... Tuberculosis Campaign. From Greece ...e have the results of surveys of allergy ...-children vaccinated in the International ... Campaign.

The ... used was the standard Danish vaccine ... Seruminstitut, and in some instances the ...es were used in all three countries. In each ...ne year after vaccination, several thousand ...ere tuberculin-tested by special teams trained ...sure reactions accurately and objectively without ...rpreting them as positive or negative. One important ...ference in technique must be mentioned: in Egypt ...e 5 T.U. Mantoux test was used instead of 10 T.U. as in Denmark and Greece.

The observations summarised in fig. 2 have two striking features. First, the curves differ in shape from that shown in fig. 1. For each country the reactions are grouped rather *symmetrically around a single central value*, and in none is there any indication of a break which might divide those successfully vaccinated from those with no alteration in their allergy. (Before vaccination, it must be remembered, the reactions of these children were in the supposedly negative range, 0–6 mm.) Secondly, *the size of the reaction is not the same in the three countries.*

In *Denmark* almost all the children showed strong post-vaccination reactions. Only a very few reactions were smaller than 8 mm. of induration; *quite a few measured more than 20 mm.*; and the average size was 16·7 mm.

In *Egypt the average size was only 5·3 mm.* (11 *mm.* less than in Denmark). About 5% of the reactions measured less than 2 mm. and relatively *few were larger than 10 mm.* ...use of a smaller test dose (5 T.U. *in Egypt compared with* ... Denmark) accounts for only a small part of the ... in the results.

...e the highest frequency of post-vaccination sensi... between the extremes of *Egypt and Denmark.* ...ge diameter of the reactions was 10·8 mm., but they ranged over almost the whole scale. There were many small ones like those found in Egypt and a few large ones like those found in Denmark.

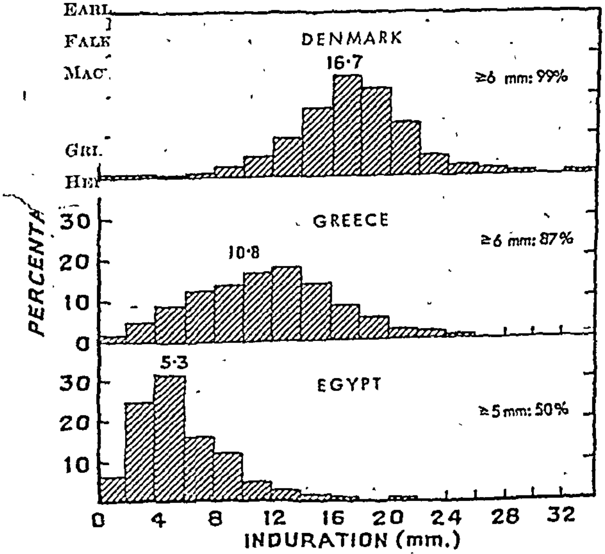

Fig. 2—Distribution of size of Mantoux reactions one year after ...accination with B.C.G., in Denmark and Greece (10 T.U.), and ...pt (5 T.U.).

TABLE I—MEAN DIAMETER OF MANTOUX 10 T.U. REACTIO... TEN WEEKS AFTER VACCINATION

Strength of vaccine	Volume of vaccine injected (ml.)		
	0·05	0·10	0·20
1/2	17·8 mm.	17·6 mm.	—
1/4	16·9 mm.	17·8 mm.	17·6 mm.
1/8	—	16·8 mm.	17·3 mm.

If the usual definition of a positive reaction were applied, 99% of the Danish, 87% of the Greek, and only 50% of the Egyptian children would be regarded as positive. But application of this definition would be completely arbitrary, for there is no break in the distributions around the 6 mm. point, or indeed at any other place, and almost all the children show some degree of allergy following vaccination. The big differences in the level of post-vaccination tuberculin sensitivity in the three countries *might be explained by*:

1. Variations in the technique of intradermal injection of the vaccine.
2. Variations in the allergy-producing potency of the vaccine—and here we might consider trauma to the vaccine, variations in dosage, viability of the organisms, and so on.
3. *Variations in the children of different racial groups*—e.g., in their physiological-immunological response to B.C.G.

On the third point studies have only recently begun, but we have investigated the first two, and I shall review some of our findings. Before leaving fig. 2, however, *I want to call attention to the fact that the average size of the reactions among children in a given group is a convenient index of post-vaccination allergy. (For the Danish children it is* 16·7 mm., *for the Greek it is* 10·8 mm., *and for the Egyptian it is* 5·3 mm.) *For most of the following material, therefore, I shall use simply the average size of reactions to express results.*

TABLE II—MEAN DIAMETER OF MANTOUX 10 T.U. REACTIONS TEN WEEKS AFTER VACCINATION

Depth of Injection	Mean diameter of reactions (mm.)
Intracutaneous, superficial	19·9
Intracutaneous, intermediate	20·0
Intracutaneous, deep	19·3
"Subcutaneous"	19·3

VARIATIONS IN THE TECHNIQUE OF INTRADERMAL INJECTIONS

There are two simple errors of which vaccinators using the intradermal method might be guilty:

1. Either more or less than the specified 0·1 ml. of vaccine might be injected.
2. The vaccine might be injected rather deeply, even into the subcutaneous tissue, instead of superficially as recommended.

Table I shows the effect on post-vaccination allergy of varying the volume of vaccine injected. Using dilutions of 1/2, 1/4, and 1/8 standard strength, injections of 0·05, 0·1, and 0·2 ml. were given—i.e., half the volume ordinarily used, the full volume, and twice the volume. Altogether seven comparable groups (each of some 80 children) were vaccinated, each group with a different combination of strength and volume of vaccine. As the table shows, the average size of the tuberculin reaction ten weeks after vaccination was unaffected by such variations in the volume of vaccine injected. Table II ows the effect of changing the depth of injection. efore this study was begun, one of our field nurses actised on the office staff until she became expert varying the depth of injections: she was able to ject at four different degrees of depth, from very perficially (just into the skin) to relatively deep lmost if not actually into the subcutaneous tissues). he results based on tests of over 200 children show at the depth of the injection of tuberculin did not gnificantly affect the size of the reaction.

The range of depths and volumes of injection which e chose for the above tests was intended to encompass ost of the variations in technique which one might nd among different vaccinators. Only rarely would ore than 0·2 ml. or less than 0·05 ml. be injected, nless vaccinators were careless about their work. The ests convinced us that minor variations in technique ave little effect on the allergic response, and cannot explain the different results obtained in Denmark, Greece, Egypt and other countries.

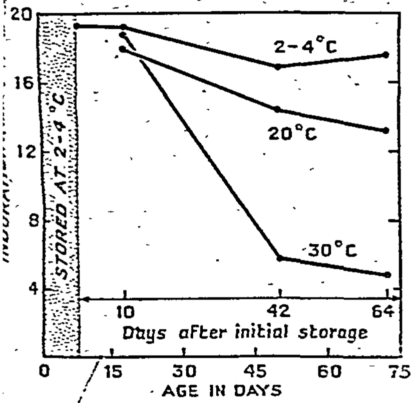

Fig. 3—Mean size of Mantoux 10 T.U. reactions two months after vaccination with B.C.G. stored for various periods at various temperatures.

VARIATIONS IN THE ALLERGENIC POTENCY OF THE VACCINE

Effect of Time and Temperature of Storage

In the past it has been held that B.C.G. vaccine must be kept cold and used within a few days of preparation. Since in actual practice it may not always be possible to keep this rule, we have tried to determine the effect of time and temperature of storage on the allergy-producing potency of the vaccine.

Fig. 3 shows the results obtained with a single batch of Danish vaccine which was stored for eight days at a temperature of 2°–4°C, and was then divided into three parts which were stored at 2–4°, 20°, and 30°C. Samples of these preparations were then used ten days, forty-two days, and sixty-four days later, and the children receiving them were tuberculin-tested two months after vaccination. It will be seen that when vaccine was used after an initial eight-day period of storage at 2°–4°C, the average size of tuberculin reactions was nearly 20 mm. When the vaccine was kept cold for an additional ten days, there was essentially no change in the allergy produced. The average size of the reaction was slightly smaller when vaccine stored cold for forty-two days was used; but even with vaccine stored for two months the diminution was not of any consequence.

Storage at room-temperature (20°C) certainly did reduce the capacity of the B.C.G. to produce allergy, but even when the vaccine was stored at this temperature for two months the average size of induration was about 14 mm.—an entirely satisfactory tuberculin reaction, by accepted standards.

After about a week of storage at 30°C, the vaccine had apparently lost none of it potency, for the average size of the tuberculin reactions of children vaccinated with this sample was nearly 19 mm. Six weeks' storage at this temperature, however, reduced the average size of the reactions to about 5 mm—i.e., about the same as that of the Egyptian children.

Had the results shown in fig. 3 been expressed, not in average size of reactions, but, as is more customary, in percentage of "positive" reactions, we should have found 100% positive among the children vaccinated with B.C.G. stored for as long as two months at 2–4° or 20°C, or for a week at 30°C. Only the sample stored at 30°C for a month or more would have shown less than 100% "positive" reactions. But by measuring the reactions, and expressing the data in terms of distributions or average size of reaction, it is possible to demonstrate quite clearly what effect temperature and length of storage have on the vaccination results.

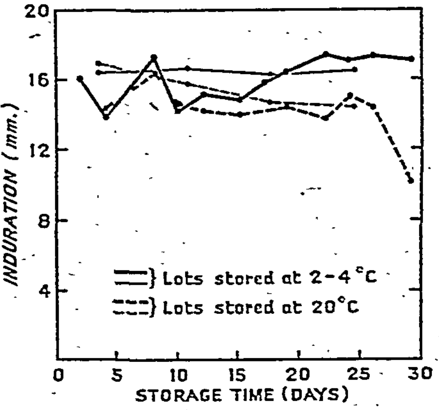

Fig. 4—Mean size of Mantoux 10 T.U. reactions one year after vaccination with B.C.G. stored for various periods at 2–4°C and at 20°C.

When results like these were first obtained, we were told that the allergy produced by vaccine more than two weeks old—especially that produced by vaccine kept so long at room-temperature—would be only temporary. This was not so. Fig. 4 shows the average size of tuberculin reactions *one year after vaccination* with samples of vaccine stored at 2–4° and 20°C, and used every few days for a month. Admittedly the children vaccinated with B.C.G. stored at 20°C did not show quite as strong an allergic response as those receiving vaccine stored at 2°–4°C, but the difference is of no practical importance.

These results demonstrate that B.C.G. vaccine can be kept for relatively long periods, and stored at moderate temperatures, without much loss of allergy-producing potency. We have repeated the work many times, with many different vaccines, and have obtained essentially the same results; so we are confident they represent the facts for the various vaccines studied. Some of these same batches were used in the campaigns in Egypt, Greece, and other countries. It is difficult, therefore, to attribute the low allergy observed in these countries

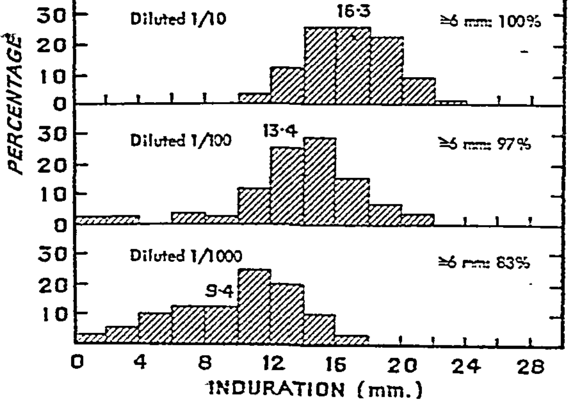

Fig. 5—Distribution of size of Mantoux 10 T.U. reactions two months after vaccination with standard Danish B.C.G. in various dilutions.

to temperature or to the length of time the vaccine was stored—especially difficult because the B.C.G. campaigns rarely used vaccines more than two weeks after their preparation, and great efforts were always made to keep them cold.

Effect of Diluting the Vaccine

We also tried varying the strengths of B.C.G. vaccine. There are a number of reasons why investigations of this subject are important:

1. Inevitably there is some variation in the strength of different 0·1 ml. injections of vaccine. Because the vaccine is a suspension of B.C.G. organisms which must be shaken or mixed before use, the concentration of different doses may differ considerably if it is not mixed carefully.

2. Different laboratories issue different concentrations of B.C.G. organisms by weight per unit volume, and there is little agreement on the amount needed for a successful vaccination.

3. Changing the weight of B.C.G. organisms per unit volume is an everyday method for increasing or decreasing the potency of the vaccine.

Very interesting results were obtained when the dosage or strength of B.C.G. was varied simply by diluting the vaccine. At first we used vaccine diluted to give 1/2, 1/4, and 1/8 of a standard dose in the usual 0·1 ml. injection. Next we used vaccine diluted 1/4, 1/16, 1/64, 1/128, and 1/256 of the usual amount. Still later, dilutions using 1/1000 of the standard dose were given, and plans are now being made to vaccinate with doses of 1/10,000 and 1/100,000 of the usual dose.

Fig. 5 gives the results of Mantoux 10 T.U. tests two months after vaccination. The top section shows the size of reactions after vaccination with standard Danish vaccine, prepared to contain 0·75 mg. of B.C.G. per ml., while the second, third, and lowest sections show their size when the standard vaccine was diluted 10 times, 100 times, and 1000 times. The averages in these four groups were 18·5 mm., 16·3 mm., 13·4 mm., and 9·4 mm.; so it is clear that progressive dilutions of the vaccine, and correspondingly smaller doses of B.C.G., do produce a progressive decrease in the degree of post-vaccination allergy.

This chart shows again why it may be misleading to express the results of B.C.G. vaccination in terms of "positive" reactors. If we had simply classified the reactions as either positive or negative, we should have found 100% positive for both standard and 1/10 vaccines, 97% positive for 1/100, and 83% positive for 1/1000. In fact, there would be almost no difference in the percentage of positives until the vaccine had been diluted 1000 times.

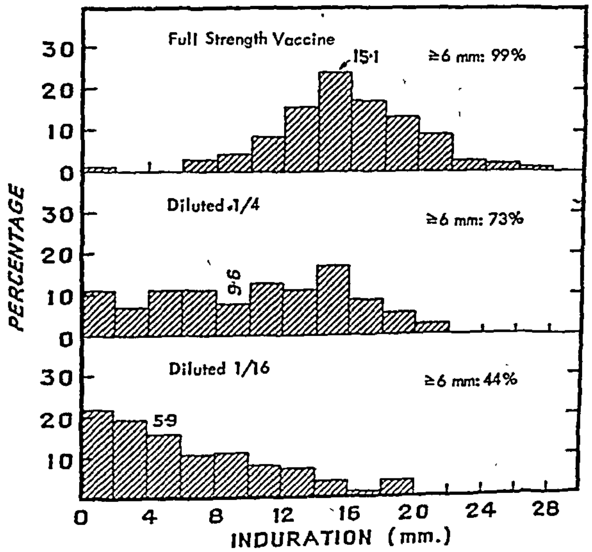

Fig. 6—Distribution of size of Mantoux 10 T.U. reactions two months after vaccination with another standard preparation of B.C.G. in various dilutions.

To illustrate the danger of drawing conclusions about B.C.G. from one single study, I shall give the results of a second piece of work on the effect of diluting the vaccine, using this time a standard preparation from a different laboratory. Fig. 6 summarises reactions to Mantoux 10 T.U. two months after vaccination with this vaccine at full strength and diluted 1/4 and 1/16. With the standard strength the average size of the reaction was 15·1 mm., which was less than that produced with the 1/10 dilution of the Danish standard vaccine (fig. 5). More important here, however, is the fact that, with this second vaccine, dilution had a much greater effect on potency. Diluted 16 times, it produced tuberculin reactions averaging only 5·9 mm. in diameter.

During the past two years further studies have been made with diluted vaccines, and fig. 7 gives some of the results. Each line on the chart represents a different batch of B.C.G. vaccine. In full strength (1/1) these vaccines differed little in potency: the average reaction was about 18·5 mm. with vaccine *a* and just over 15 mm. with vaccine *f*. But on dilution the differences increased, and it will be seen that the 1/8 dilution of vaccine *f* gave about the same reaction (9–10 mm.) as the 1/1000 dilution of vaccine *b*. The reason why the curves are not parallel may be either (1) unrecognised *qualitative* differences in the vaccines, or (2) unrecognised variations in the preparation of vaccines, causing a varying amount of damage to the living tubercle bacilli. But, whatever the explanation, it is clear that one vaccine cannot always be made comparable with another simply by changing the amount of B.C.G. contained per dose.

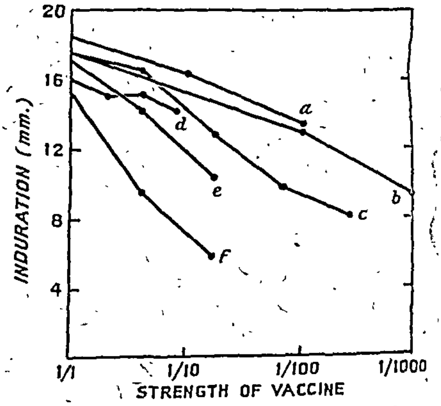

Fig. 7—Mean size of Mantoux 10 T.U. reactions two to three months after vaccination with different batches of B.C.G. (a–f) in various dilutions.

Before leaving this chart I should like to point out that we are dealing here with the effect of very substantial dilutions—e.g., 1/1000 for some of the vaccines shown. *Small* differences in concentration, on the other hand, cause practically no change in allergy production. Even with vaccine *f*, which has the steepest decrement, dilution to 1/2 reduces the average size of reaction by only 1 or 2 mm., and with the other vaccines similar dilution would not cause even this slight change. The success or failure of a vaccine cannot be attributed to these minor differences.

In the autumn of 1949 Statens Seruminstitut created some consternation locally when they increased the weight of B.C.G. in their routine vaccine by 50% (from 0·5 to 0·75 mg. per ml.); but it now seems unlikely that so small a change had the slightest influence on its allergy-producing potency. This conclusion is supported by our studies (table I) in which the volume of vaccine injected was varied from half a dose (0·05 ml.) to four times that amount (0·2 ml.) without any definite change in allergy production.

fect of Varying oportions of at-killed and ving Vaccine

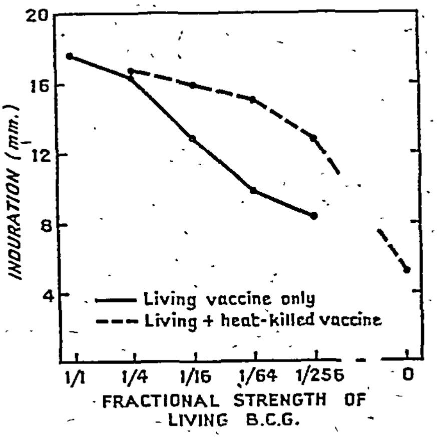

Fig. 8—Mean size of Mantoux 10 T.U. reactions ten weeks after vaccination with living vaccine and with living + heat-killed vaccine.

Perhaps our ost interesting d important idies are those the relative fects of living d dead B.C.G. ccine. The oduct for this ork was stand- d Danish vac- ne, diluted in rying propor- ons with vac- ne which had en heated to)°C for two ours to kill the organisms.‡ For example, we mixed ifferent proportions of living and heat-killed vaccines obtain a vaccine which was of standard strength but which some of the organisms were presumably dead nd the rest were presumably living. In this way we ere able to vaccinate groups of children with standard- rength vaccine containing different fractional propor- ons of living organisms. Other groups were vaccinated ith the same fractional strengths of living vaccine *ithout* the addition of any heat-killed B.C.G.

In fig. 8 the solid line shows the results of a Mantoux 0 T.U. test ten weeks after vaccination with living accines without the addition of any heat-killed vaccine: he reactions averaged about 18 mm. in diameter with ull-strength living B.C.G.; their size was 16 mm. with accine diluted 1/4; and they decreased progressively n size when the vaccine was diluted 1/16, 1/64, and 1/256. The broken line shows the reactions (also at ten weeks) with fractional proportions of living vaccines made up to full concentration by adding heat-killed vaccine. These results surprised us. There was no difference at all between the effect of vaccine diluted four times with dilute Sauton culture medium and the same vaccine diluted four times with heat-killed vaccine. As the proportion of living B.C.G. is decreased, however, the effect of the heat-killed component becomes more pronounced. The striking finding here is that heat-killed vaccine, with the addition of just a leavening of living B.C.G., produced good allergy: thus vaccine composed of 1 part living vaccine and 255 parts heat-killed gave an average of about 13 mm. of induration.

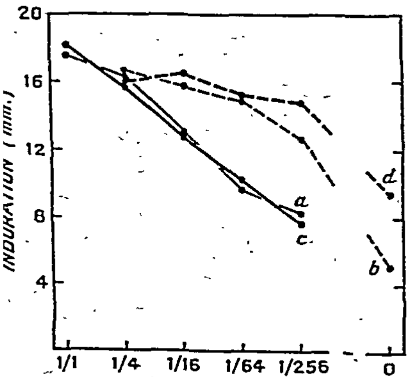

Fig. 9—Mean size of Mantoux 10 T.U. reactions after vaccination with B.C.G.

(a) Living vaccine only. (b) Living + heat-killed vaccine. } Mantoux test ten weeks after vaccination

(c) Living vaccine only. (d) Living + heat-killed vaccine. } Mantoux test one year after vaccination

But when *only heat-killed vaccine* was used, the average size of the tuberculin reactions dropped to 5 mm.—about the same as that found in Egyptian children vaccinated with standard (and presumably) living vaccine in the mass campaign!

To check the opinion advanced by some of our colleagues that allergy produced by dead vaccine (or mostly dead vaccine) would be transient, the children in this study were retested one year after vaccination. Again the results were unexpected. The allergy produced by the fractional amounts of living B.C.G. was almost exactly the same after one year as it had been after ten weeks: in fig. 9 line *c* is practically superimposed on line *a*. The allergy found at ten weeks was not lost by the end of one year, as some had predicted; on the contrary, it actually increased in the children given partly dead vaccine. For example, children receiving vaccine composed of 255 parts of heat-killed and only 1 part of standard living vaccine had reactions averaging 13 mm. after ten weeks, and 15 mm. after a year—a result about as good as had been obtained with some batches of standard full-strength living vaccine. More interesting still is the fact that the average reaction of children receiving standard vaccine, which had been heated to 80°C for two hours, increased from about 5 mm. at ten weeks to more than 9 mm. at one year.

In reporting these results I must emphasise that we are dealing here only with the allergy-producing properties of vaccines: and these may not be a measure of their immunising effects. It may well be that fractional strengths of living vaccine, and different combinations of living and dead vaccines, differ far more in their immunising potency than might be inferred from their ability to induce allergy. How little do we really know about immunisation!

Effect of Exposure to Sunlight upon B.C.G.§

A great many biological products are harmed by the effects of light, and, without any direct evidence that this also applies to B.C.G., the opinion has been expressed from time to time that undue exposure of the vaccine should be avoided. Very recently this question has been studied in the Tuberculosis Research Office, and the preliminary results show that light has a devastating effect on B.C.G. vaccine. One hour's exposure to Danish sunshine of low actinic value resulted in a drop in the colony count from over 9,000,000 to about 9000 per ml. and a consequent reduction in the average size of the Mantoux reactions from 19·5 mm. to 9·6 mm.

Could it be then that the vaccines sent to Egypt and other countries were light-killed before they reached their intradermal destinations? Work is now in progress on this very point. Twice as many vials as necessary have been sent to Egypt and exposed to field conditions at the vaccination centres, after which every second vial has been returned unbroached to its container and sent back to Copenhagen for study.

While it is still too early to say, it now seems possible that many of the unexpected results of vaccination projects throughout the world may be due to the traumatic effect of light on the vaccine.

CONCLUDING REMARKS

I said at the beginning that our results have proved different from what we expected, and from what has been generally taught. For example, it was taught that the intradermal method of vaccination is better than any other because an exact dose of B.C.G. can be given. It was taught that B.C.G. vaccine has to be kept cold and used within a very short time after preparation. It was taught that large numbers of living B.C.G. organisms are needed to obtain a satisfactory allergic response among the vaccinated, and that the potency of a given vaccine can be adjusted simply by minor changes in the amount of B.C.G. per unit volume. A certain level of tuberculin allergy has been accepted as evidence of successful vaccination, and reactions above and below that level have been called positive and negative.

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‡ Although this procedure was designed to kill all B.C.G. organisms in the vaccine, it has been possible, occasionally, to culture a few viable organisms from undiluted samples, but these survivors represent about half-dozen out of some 9,000,000!

§ This section was not included in the lecture when it was given in Oslo. See *Bull. World Hlth. Org.* 1952, 5, 245, 333.

I would not presume to say that all our anomalous findings will be confirmed or that we have intepreted them correctly; but I think that most of them will survive. Certainly it is evident that much of what we have accepted as common knowledge about B.C.G. vaccine and vaccination is not very well founded; and, if so much of what we thought we knew of the simpler facts be untrue, what can we safely believe about those aspects of vaccination which are more difficult to study and to prove?

I think we can safely believe in the ultimate efficacy of tuberculosis immunisation. We can also, I think, unhesitatingly support mass B.C.G. vaccination programmes in many countries in the world where vaccination is almost all that can be done today to control tuberculosis. B.C.G. is certainly the best known, the most promising, and the most acceptable immunising agent at our disposal. On the other hand, we must seek more dependable information about B.C.G. and tuberculosis immunisation. And this may mean discarding many of our traditional concepts.

STANDARDS FOR THE BASAL METABOLISM OF NORMAL PEOPLE IN BRITAIN

J. DOUGLAS ROBERTSON
M.D., D.Sc. St. And., F.R.C.P., F.R.I.C., D.P.H.
DIRECTOR, DEPARTMENT OF CLINICAL INVESTIGATION, THE LONDON CLINIC

D. D. REID
M.D. Aberd., Ph.D. Lond.
READER IN EPIDEMIOLOGY AND VITAL STATISTICS, LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

THIS study was begun at the Middlesex Hospital in 1930, as a direct result of observations on variations in the basal metabolic rate (B.M.R.) in thyrotoxicosis before and after treatment with iodine and before and after subtotal thyroidectomy.

It was noted that, after a successful subtotal thyroidectomy and in the absence of any clinical manifestations of hypothyroidism, the B.M.R., by the standards of Aub and DuBois (1917), was never above 0, and all values lay between 0 and −20. To determine whether or not such a low postoperative range was a natural sequence of removal of the thyroid gland in thyrotoxicosis, a group of fifty nurses in training at the Middlesex Hospital volunteered to have their B.M.R. measured. Their rates also were between 0 and −20. It became apparent that either the standards of Aub and DuBois were too high for people in this country, or that there were some differences in technique in measuring the B.M.R., or both. As there were no British standards for the B.M.R. based on actual measurements taken in this country over a wide range of ages in both sexes, it was decided to begin such a study.

The value of any standard with which a patient's results can be compared depends on the consistency of technique between the workers setting up that standard and those who later use it as a basis for comparison. For convenience we outline below the standard technique adopted, although it has already been described in detail (Robertson 1944).

STANDARD TECHNIQUE OF MEASUREMENT OF B.M.R.

The closed-circuit method was employed, the accuracy of which has already been reported (Robertson 1937). The apparatus used was the Benedict-Roth with recording kymograph. All the machines were alcohol-checked (Barrett and Robertson 1937), but also, each machine was checked once a week by B.M.R. estimations on the same healthy female whose heat output was constant when corrected for age.

Attendance of the people included in this survey was required after the customary fast of at least twelve hours; the last meal had to consist of an egg (or an equivalent amount of protein), bread and butter, and weak tea. The person was weighed on a machine of the fulcrum type, which was repeatedly checked for accuracy. An allowance of 3½ lb. was made for the weight of the trousers, shirt, and underwear worn by men, and 2½ lb. for the dress and underwear of women, so that estimated nude weights could be used to calculate the surface area of the body. This area was found by applying the formula using height and weight which was originally produced for this purpose by DuBois and DuBois (1916) and approved by Boothby et al. (1936).

After half an hour's rest on a comfortable bed in a quiet room at a temperature of 20°C, duplicate determinations were made of the heat output, and the result was expressed as calories per square metre of body-surface per hour. Similar determinations were made on the next day, when the results were commonly lower than those obtained on the first day. This procedure was continued until no further fall in the heat output was observed—i.e., until the second of the two duplicate readings differed by no more than 5% from the first duplicate on the same day. It should be noted that in these estimations independent readings of the spirogram were made by two or more observers. The test was repeated when the two observers did not agree; in this way it was hoped to avoid a consistent personal bias.

In this study the lowest reading observed in the series was taken as an estimate of the true basal level of metabolism. As Vogelius (1945) has shown, graphs of the results of repeated estimations reveal a clear training

TABLE I—OBSERVED HEAT OUTPUT AT SPECIFIED AGES
(Calories per square metre body-surface per hour)

Age last birthday (yr.)	Males			Females		
	No. of persons	Mean heat output	Standard deviation	No. of persons	Mean heat output	Standard deviation
3	6	61·0	7·27	6	51·8	3·60
4	34	58·1	4·90	24	52·6	4·07
5	33	51·2	5·21	41	53·3	5·11
6	48	53·8	1·31	28	52·1	3·35
7	27	51·3	3·32	27	51·1	3·14
8	21	49·5	5·00	18	47·2	4·14
9	13	50·0	4·97	30	45·2	3·68
10	16	47·9	4·51	13	45·3	3·66
11	34	47·7	3·77	18	43·0	3·97
12	41	43·5	3·82	31	40·5	3·48
13	30	42·2	3·74	39	38·2	2·99
14	33	42·8	3·41	36	37·3	2·67
15	20	41·0	2·67	33	36·7	2·54
16	24	39·6	3·41	21	35·4	2·90
17	24	39·0	3·29	22	35·4	2·72
18	21	39·5	3·37	32	35·2	2·24
19	22	38·9	2·58	224	34·7	2·50
20	42	38·2	2·26	116	34·3	2·35
21	15	37·8	1·90	50	34·5	2·17
22	19	36·7	2·13	35	33·7	2·10
23	14	37·5	3·01	30	33·8	1·83
24	19	37·5	2·48	26	33·8	2·72
25	21	36·8	3·06	31	33·4	2·60
26	21	37·0	2·85	14	34·1	1·61
27	33	37·1	2·61	18	34·4	2·33
28	30	37·3	2·10	25	34·0	2·08
29	29	36·7	2·47	17	33·8	2·13
30	28	36·8	2·15	15	34·1	2·20
31	24	36·5	2·50	16	34·0	2·18
32	21	37·0	2·38	15	34·5	2·75
33	27	35·8	2·36	8	34·0	2·07
34	21	35·0	2·20	21	33·4	2·06
35	21	36·0	2·20	12	33·6	1·38
36	20	35·6	2·37	11	32·8	2·09
37	19	35·9	2·99	20	34·2	1·98
38	10	35·4	2·80	16	32·3	2·98
39	13	35·2	2·48	21	32·3	2·18
40	22	36·1	2·08	21	32·8	2·84
41–44	19	34·9	2·61	37	32·5	2·30
45–49	11	34·1	2·70	36	34·3	2·69
50–54	11	34·5	2·54	25	34·9	2·35
55–59	6	33·5	3·21	6	30·2	1·47
60–64	8	32·5	1·85	10	32·3	1·83
65–69	9	32·2	2·19	17	30·3	1·65
70–74	4	33·3	3·10	8	30·5	1·60
75 or more	3	32·0	3·16	..	..	..

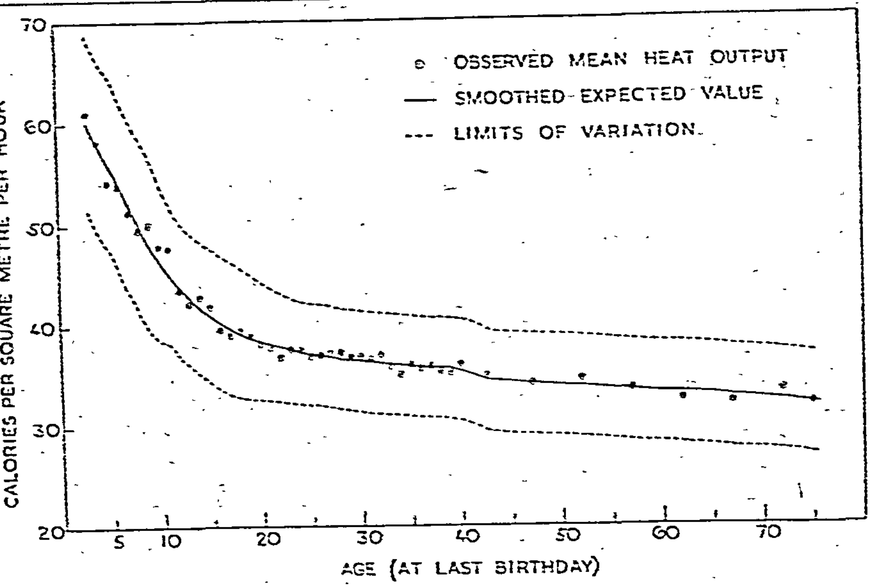


Fig. 1—Observed and expected mean heat outputs at ages and limits of variation (males).

effect: successive readings fall rapidly at first, but after about the first four estimations the curve describing the trend of results flattens out quickly. It seems reasonable therefore to take either the lowest recorded value or the mean of the last two readings made as an estimate of the asymptote or basal metabolic level which the curve is approaching. It could be argued that where the latest is also the lowest value in a short series of four readings it is more likely to be nearer to the true basal level than the mean of the third and fourth readings. On the other hand, in longer series, where the curve has flattened out, the mean might be the more appropriate indicator of the basal level. Since in practice we are here dealing with shorter rather than longer series, and since too we accept that stabilisation has been reached only when the last two readings differ by less than 5%, the difference between taking the lower of the two rather than their average is relatively small.

This method of repeating observations until stability is apparently achieved is in contrast to the usage adopted by Boothby et al. (1936), whose paper on standards for B.M.R. in normal people appeared while this work was in progress. They took as their basal value "the first determination made for the individual unless at the time of the test and before its calculation it was noted as unsatisfactory for reasons of restlessness, observable nervous tension, or an elevated temperature." They criticised the policy of taking several readings and maintained that results would vary according to the number of readings taken. Thus, even if several readings were taken on a subject, the first only was used for computing their normal standards. They further stated that "if one departs from the practice of using a single determination made under standard conditions, the number of determinations should strictly be identical for each individual." Thus the element of training was excluded from their normal standards as they suggested it would be in its clinical application.

Robertson (1944) has criticised these views on the following grounds:

(1) So-called nervous tension is not uncommon at the initial test, particularly in thyrotoxicosis.

(2) Initial readings are commonly higher, and sometimes much higher, than subsequent or true basal determinations. Thus of 223 people aged 19, 156 (70%) gave initial readings which were higher than those on the second day, 48 (22%) gave results 10% or more higher, 21 (9%) gave results 15% or more higher, and 11 (5%) gave readings as elevated as 20% or more higher. In no case was the initial reading at the time of test considered unsatisfactory, and a kymographic record of the respirations is a very sensitive guide. These observations were made on nurses who had volunteered for the test; apprehension is much more likely in nervous patients, with or without thyrotoxicosis. To estimate a person's B.M.R. on the initial observation alone is to run the risk of reporting a raised B.M.R. as due to pathological rather than psychological causes.

(3) If standards are based on initial readings alone, the metabolic assessment of people who have ever had the test before presents a problem, since to have had experience of the test means some degree of the training which Boothby and his colleagues suggested should be excluded.

(4) The controlling influence of iodine on the B.M.R. in thyrotoxicosis as a diagnostic test becomes much less sensitive; for indeed it would be difficult to determine whether a fall in the B.M.R. in a subsequent test after iodine was due to the element of training or to iodine.

In this study of the basal energy output of 987 males and 1323 females, aged between 3 and 80 years, we have followed the convention also adopted for the American standards by Boothby and his colleagues by expressing this basal output in terms of calories per square metre of body-surface per hour. Justifiable objections have been raised to the use of such per-weight and per-surface-area standards (e.g., by Tanner 1949) on the grounds that they imply that heat output always bears a constant ratio to surface area. It is perhaps fortunate that, for the limited range of values within a single age and sex

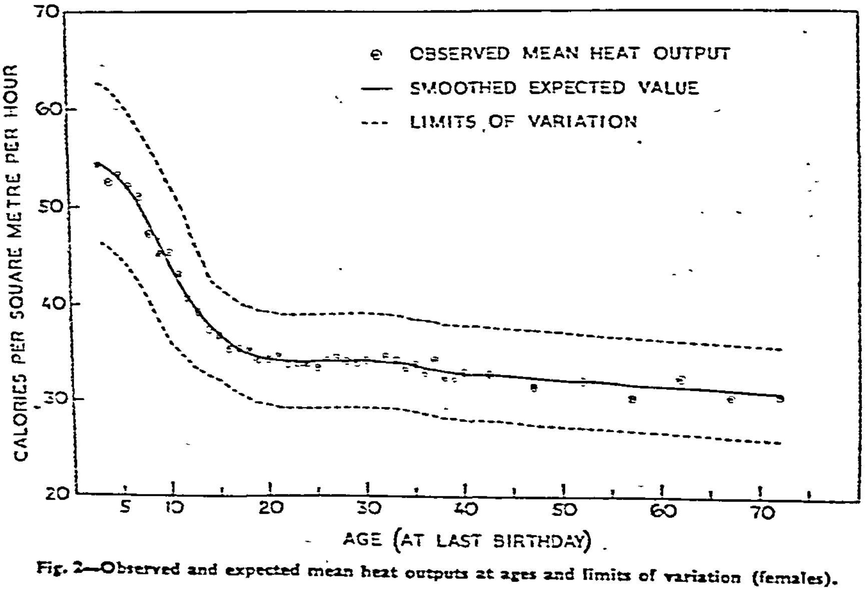


Fig. 2—Observed and expected mean heat outputs at ages and limits of variation (females).

group, the relation between heat output and surface area described by the regression line of output on area is approximated reasonably well by the assumption of a constant ratio between the two biological measurements. From the practical point of view, therefore, it is legitimate to compare the ratio of heat output to surface area in a person with the mean and likely range of similar ratios for a group of healthy people of the same sex and age.

Clearly, no method of estimating and expressing the level of metabolic activity in a simple practical but unexceptionable way has yet been evolved. It must be remembered that the standards set up by this study refer to a B.M.R. measured under standard conditions by standard methods which, although they may not be theoretically perfect, at least have the essential merit of consistency, since all the observations were made by one of us (J. D. R.) between 1930 and 1950.

TABULATION OF RESULTS

As already mentioned, the basal heat output is expressed as a ratio to the surface area derived from height and weight. The mean number of calories per square metre per hour has been calculated for members of each sex for each year of age between 3 and 40 years, and these means are set out in table I. For those aged more than 40, observations were grouped into 5-year age-groups. Plotting these means gave the pattern seen in figs. 1 and 2. Compared with a similar curve from the American standard data, it shows much less irregularity, particularly for the years of adolescence, but the same tendency to asymptote at ages over 40.

An attempt was therefore made to describe these observations by one curve for each sex extending over the age range 3–40 for which individual year means were available. Changes in metabolic activity with increasing age may well be regarded as a growth phenomenon, and it seemed biologically reasonable to use a logistic curve for the fitting process. Clearly too, no simple logistic would fit the apparent changes in the speed of metabolic adaptation at different ages. According to the methods suggested by Pearl (1940) a skew logistic curve with a quintic exponent was fitted to the data, with the result seen in figs. 1 and 2. For males (fig. 1), where the numbers in each group were fairly equal, no weighting was needed; but for females (fig. 2) the means at ages were weighted by the numbers of observations upon which they were based. The resultant fit is quite adequate; the analysis of variance for each sex for the age range between 3 and 40 displayed in table II shows that the residual variation not accounted for by the fitted regression line differs insignificantly from the error variance.

TABLE II—TESTS FOR GOODNESS OF FIT OF CURVE TO OBSERVED HEAT OUTPUT

Analysis of variance				
Sex	Source of variation	Sum of squares	D.F.	Mean square
Males: Aged 3–40 yr.	Fitting of logistic	43,445·99	7	6206·57
	Deviations from logistic	350·49	30	11·68
	Within age-group	9119·44	878	10·39
	Total	52,915·92	915	..
Aged 41 and over	Fitting straight line	57·09	1	57·09
	Deviations from line	12·63	6	2·11
	Within age-group	441·24	63	7·04
	Total	510·96	70	..
Females: Aged 3–40 yr.	Fitting logistic	38,525·43	7	5503·63
	Deviations from logistic	281·87	30	9·40
	Within age-group	9181·33	1146	8·01
	Total	47988·63	1183	..
Aged 41 and over	Fitting straight line	52·17	1	52·17
	Deviations from line	40·84	5	8·17
	Within age-group	679·10	132	5·15
	Total	772·11	138	..

It might be pointed out in passing that the skew form of the logistic curve used to achieve this fit is supposedly more appropriate to the growth of collections of cells whose speed of multiplication is subject to some central control than to the increase in size of a population of independent units—e.g., to the growth in size of a person rather than to a rise in a population. In other words, the methods used in this study to measure the change with increasing age of individuals' B.M.R. appear to produce results which are at least consistent with rational expectation. In this respect they differ from the results obtained by Boothby et al. (1936), where the result of the first test is used as an indicator of the basal level of metabolic activity. For ages over 40 a straight line gave a good fit to the trend of the mean heat output per square metre per hour in both sexes.

The smoothed values, which are supposedly free from erratic sources of variation, could be derived from the formulæ thus used to describe the data:

For males (aged 3–40)

$$\text{Heat output is cals./sq. m./hr.} = 30 + \frac{35}{1 + e^{u}/10}$$

where $u = 1{\cdot}3724343 + 0{\cdot}54564663x - 0{\cdot}027774833x^2 + 0{\cdot}0^3 76481273x^3 - 0{\cdot}0^4 10880471x^4 + 0{\cdot}0^7 62750139x^5$, and x is age in years.

For males (aged 41 or more)

$$\text{Heat output} = 37{\cdot}405365 - 0{\cdot}06944x.$$

For females (aged 3–40)

$$\text{Heat output} = 30 + \frac{30}{1 + e^{u}/10}$$

where $u = 0{\cdot}9683040 - 0{\cdot}22383820x + 0{\cdot}0685533x^2 - 0{\cdot}0^2 40652313x^3 + 0{\cdot}0^4 95117564x^4 - 0{\cdot}0^6 78506248x^5$.

For females (aged 41 or more)

$$\text{Heat output} = 35{\cdot}15375 - 0{\cdot}06149x.$$

In practice, however, it is simplest to refer to the tabulated values for each year of age given in table III. By themselves, of course, the means give no indication of the range and frequency distribution of deviations from this "normal" average. The standard deviation, which is the best measure of this variability between persons of the same age, declines in size from birth until adolescence in both sexes and is fairly constant in adult life. Stability is reached earlier in females among whom the variances in the age-groups from 13 onwards are shown by the Bartlett test to differ insignificantly. Similarly the within age-group variances at ages between 3 and 12 years do not differ appreciably. Standard deviations have been calculated from variances based on all the observations within these homogeneous segments of the age scale, and they have been used, after appropriate smoothing at the junction of the two segments, to mark the "control limits" seen in fig. 1. For males three homogeneous sections were found at 3–10 years, 11–20 years, and 21 and over, and similar "control limits" have been derived from the standard deviations based on all observations within these age-groups.

In the practical use of these results it is most convenient to refer to table III, where the mean heat output in calories per square metre of body-surface per hour is set out for healthy people of a specified sex and age together with the corresponding limits of usual variation between people in the same age-group. These "control limits," which correspond to heat outputs two standard deviations above and below the expected mean, mark the values between which should lie most (95%) of such readings made on healthy people of that sex and age. If the patient's basal heat-output rate is outside these limits it may be regarded as significantly unusual and therefore potentially pathological. Thus we might have a male patient aged 29 whose heat output per square metre per hour is 39 calories. We note that, although this differs by 2·5 calories from the expected or normal average of 36·5 calories, the divergence is equal to the standard deviation of 2·5 calories; hence the patient's test result lies within the limits of normal variation. Only if the output were greater than 41·5 or less than 31·5 would we suggest, on this evidence alone, that the patient's B.M.R. was abnormal in the sense here used.

These standards are based upon observations made on apparently healthy volunteers. These were nurses, medical students, and members of the staff of the Middlesex Hospital, children attending welfare clinics and on tonsillectomy waiting-lists, and members of the public who came in response to newspaper appeals. In so far as these "normal people" are typical of the British population, these tables of their heat output at different ages, measured by the technique described, should form a useful standard for clinical work on basal metabolism in this country.

TABLE III—EXPECTED MEAN HEAT OUTPUT AND LIMITS OF VARIATION

(Calories per square metre body-surface area per hour)

Age last birthday (yr.)	Males			Females		
	Expected mean	Lower limit	Upper limit	Expected mean	Lower limit	Upper limit
3	60·1	51·5	68·8	54·5	46·4	62·6
4	57·9	49·2	66·5	53·9	45·8	62·1
5	56·3	47·7	65·0	53·0	44·9	61·1
6	54·2	45·6	62·8	51·8	43·6	59·9
7	52·1	43·4	60·7	50·2	42·1	58·3
8	50·1	41·4	58·7	48·4	40·2	56·5
9	48·2	39·6	56·7	46·4	38·2	54·5
10	46·6	38·6	54·4	44·3	36·3	52·5
11	45·1	37·7	52·2	42·4	35·1	50·6
12	43·8	36·8	50·4	40·6	34·0	47·7
13	42·7	36·0	49·3	39·1	33·2	45·1
14	41·8	35·2	48·4	37·8	32·6	42·7
15	41·0	34·4	47·6	36·8	32·2	41·7
16	40·3	33·7	46·9	36·0	31·3	40·8
17	39·7	33·1	46·3	35·3	30·7	40·2
18	39·2	32·9	45·6	34·9	30·1	39·7
19	38·8	32·7	45·0	34·5	29·7	39·3
20	38·4	32·6	44·3	34·3	29·5	39·1
21	38·1	32·5	43·7	34·1	29·3	38·9
22	37·8	32·4	43·1	34·0	29·2	38·8
23	37·6	32·3	42·6	34·0	29·1	38·8
24	37·3	32·2	42·3	33·9	29·1	38·8
25	37·1	32·1	42·1	34·0	29·1	38·8
26	37·0	32·0	42·0	34·0	29·2	38·8
27	36·8	31·8	41·8	34·0	29·2	38·8
28	36·6	31·6	41·6	34·0	29·2	38·9
29	36·5	31·5	41·5	34·1	29·2	38·9
30	36·4	31·4	41·4	34·1	29·2	38·9
31	36·3	31·3	41·3	34·0	29·2	38·8
32	36·2	31·2	41·2	33·9	29·1	38·8
33	36·1	31·1	41·1	33·8	29·0	38·7
34	36·0	31·0	41·0	33·7	28·9	38·5
35	35·9	30·9	40·9	33·5	28·7	38·3
36	35·8	30·8	40·8	33·3	28·5	38·2
37	35·7	30·7	40·7	33·1	28·3	38·0
38	35·7	30·7	40·7	32·9	28·0	37·7
39	35·6	30·6	40·6	32·8	28·0	37·6
40	35·5	30·5	40·5	32·6	27·8	37·5
41–44	34·5	29·5	39·5	32·5	27·7	37·4
45–49	34·1	29·1	39·1	32·2	27·4	37·1
50–54	33·8	28·8	38·8	31·9	27·1	36·7
55–59	33·4	28·4	38·4	31·6	26·8	36·4
60–64	33·1	28·1	38·1	31·3	26·5	36·1
65–69	32·7	27·7	37·7	31·0	26·2	35·8
70–74	32·4	27·4	37·4	30·7	25·9	35·5
75 or more	32·0	27·0	37·0	..	..	..

Our thanks are due to Prof. E. C. Dodds, in whose department this work was begun, and to Mr. A. V. Bridgland, Chairman of the Trustees of the London Clinic, where it was completed; to Sir Alan Daley, Mr. Somerville Hastings, and the press for their help in enlisting the coöperation of suitable people; and above all to the volunteers themselves.

REFERENCES

Aub, J. C., DuBois, E. F. (1917) *Arch. intern. Med.* 19, 823.
Barrett, J. F., Robertson, J. D. (1937) *J. Path. Bact.* 45, 555.
Boothby, W. M, Berkson, J., Dunn, H. L. (1936) *Amer. J. Physiol.* 116, 468.
DuBois, D., DuBois, E. F. (1916) *Arch. intern. Med.* 17, 863.
Pearl, R. (1940) Introduction to Medical Biometry and Statistics. 3rd ed., Philadelphia.
Robertson, J. D. (1937) *Lancet*, ii, 815.
— (1944) *Brit. med. J.* i, 617.
Tanner, J. M. (1949) *J. appl. Physiol.* 2, 1.
Vogelius, H. (1945) Basal Metabolism of Girls, 1, 617. Copenhagen.

REPAIR OF DURAL DEFECTS WITH GELATIN FILM

WYLIE McKISSOCK
O.B.E., M.S. Lond., F.R.C.S.
NEUROLOGICAL SURGEON, NATIONAL HOSPITAL, QUEEN SQUARE, AND ST. GEORGE'S HOSPITAL, LONDON

DEFECTS in the dura mater remaining after the removal of certain intracranial tumours or the excision of cortical scars have always presented a problem to the neurological surgeon because adherence of the brain to overlying structures, with subsequent formation of fibrous scar tissue, may give rise to epileptic attacks.

In attempts to prevent adhesion of the brain many different tissues have been used to close these dural defects, including fascia lata, periosteum, temporal fascia, and muscle. Likewise, the dura remaining in the wound has been split into two layers so as to bridge the defect with the extra area of membrane so produced; but though this can be done with small defects and a thick dura, it may not be possible in the frontal region, where the dura is closed thin: the larger defects provide problems insoluble by such a process.

Various foreign substances have also been used, among them 'Cellophane,' amniotic membrane, tantalum foil, fibrin foam, and 'Gel-foam' film. From the multiplicity of methods it is evident that the ideal substance has not yet been discovered.

The use of gelatin film was reported by Busch et al. (1949) but it was considered unsuitable for repairing dural defects. Weisel et al. (1950) gave a detailed account of gelatin film implanted into chest wounds as a temporary closure for pleural defects, and found that the implants were completely absorbed between the eighth and fourteenth days: tissue reaction was minimal, and the normal pleural regeneration did not seem to be hindered by the presence of the gelatin film. I compare here the results achieved with tantalum foil and with gelatin film in relation first to the postoperative convalescence and secondly to the incidence of subsequent epilepsy.

PRESENT INVESTIGATION

This series of cases dates from 1945, and in the first few years tantalum foil was used to close almost all the dural defects. Then, however, Messrs. Allen & Hanburys produced a gelatin film large enough to close the largest defects. This film is a thin transparent membrane, supplied sterilised in tubes, which closely resembles cellophane until it is moistened with saline solution, when it immediately becomes soft and is easily tucked in beneath the edges of the dural defect. No fixation of the implant appears necessary, because it sticks quite easily to the underlying brain.

The series consists of 60 cases of intracranial meningioma after the removal of which dural defects remained, 30 being treated with tantalum-foil implants and 30 with gelatin film. The series is consecutive except for half a dozen cases in which fibrin foam or film was used; these have been excluded as providing too small a number of cases to give data comparable with those of the gelatin or tantalum groups.

TABLE I—SITE OF MENINGIOMAS

Tantalum series		Gelatin series	
Frontal cortical	5	Frontal cortical	6
Parietal cortical	9	Parietal cortical	8
Parasagittal	11	Parasagittal	10
Sphenoid wing	3	Sphenoid wing	3
Temporal	2	Suprasellar	2
		Subtentorial	1
Total	30	Total	30

TABLE II—POSTOPERATIVE COMPLICATIONS

Complication	Tantalum series	Gelatin series
Temporary leak of C.S.F. from wound	8	3
Late healing	8	4
Removal of implant	6	0

The size of the defect varied considerably, but none was smaller than 4 × 4 cm.; so, if an implant had not been made, quite a large area of brain would have been exposed to the risk of adhesion to overlying bone, periosteum, or galea.

The site of the meningiomas is shown in table I.

Postoperatively there were no deaths in the tantalum series but there were 3 in the gelatin group. In none of the fatal cases was there any suggestion that the implant was at fault, for there was no evidence of infection, death being due to other causes.

An attempt has been made to assess differences in the postoperative course in the two groups by considering such items as leaks of cerebrospinal fluid (C.S.F.), late healing, and extrusion or removal of the implanted substance (see table II). There was nothing noteworthy in the temperature charts.

Late healing indicates that a given wound was not healed and dry forty-eight hours after operation, when all the sutures are normally removed. In most of these cases of late healing the wound continued to discharge a little fluid, old blood, or C.S.F., for several days. In the gelatin series all were healed within a week.

It seems evident, even from such small numbers, that the gelatin implants gave much less trouble than did the tantalum implants. No fewer than 6 patients required subsequent operation for removal of the tantalum because of persistent discharge from their wounds or because of breakdown weeks or months later from low-grade infection. In each of these 6 cases the operation revealed a mass of soft greyish granulation tissue containing pockets of pus, with the tantalum crumpled among this tissue. In 3 of the 6 cases a low-grade osteomyelitis of the bone flap had developed, and the bone flaps had to be removed. In spite of this a good new dural membrane had formed beneath the tantalum, and no patient had an infection of the intracranial contents deep to this membrane.

TABLE III—SITUATION OF TUMOUR IN RELATION TO PREOPERATIVE AND POSTOPERATIVE EPILEPSY

Tantalum				Gelatin				
Site	No. of cases	Preop. fits	Postop. fits	Site	No. of cases	Preop. fits	Postop. fits	Remarks
Frontal ..	5	2	2	Frontal ..	6	3	1	
Parietal ..	9	7	7	Parietal ..	8	3	1	(2 died)
Parasagittal	11	7	2	Parasagittal	10	5	2	
Sphenoid wing	3	2	0	Sphenoid wing	3	1	0	
Temporal ..	2	1	0	Suprasellar	2	0	1	(1 died some months later)
				Subtentorial	1	0	0	
Total ..	*30*	19	11	Total ..	30	12	5	

The gelatin series provided no example of sepsis, osteomyelitis of the bone flap, or need for removal of the implant.

Epilepsy is, of course, a common symptom in the supratentorial meningiomas, particularly where the tumour lies over the convexity of the brain or along the superior longitudinal sinus. A comparison has been made of the incidence of preoperative and postoperative epilepsy in the two groups (table III) and of recurrent and acquired epilepsy after operation (table IV), and these results have been contrasted with those described by Cushing and Eisenhardt (1938) (table V).

TABLE IV—INCIDENCE OF RECURRENT AND ACQUIRED EPILEPSY

Type of epilepsy	Tantalum (30 cases)	Gelatin (30 cases)
Preoperative	19 (*63%*)	12 (*40%*)
Recurrent	9 (*30%*)	2 (*7%*)
Acquired	2 (*7%*)	3 (*10%*)

Cushing and Eisenhardt (1938) rarely used an implant to close dural defects although they mention occasionally covering the raw brain surface with a delicate film of gutta-percha.

There is a small but probably significant decrease in both recurrent and acquired epilepsy in the present series where tantalum or gelatin have been implanted, which would suggest that some useful purpose is served by the implants. In the series of Cushing and Eisenhardt (1938) 45% of patients surviving operation continued to suffer from epilepsy, whereas the present series showed an incidence of 29% of continued seizures.

The follow-up in these cases is as yet too short for a final assessment of the continued-epilepsy rate to be made.

That this is an imperfect result all will agree, and no doubt further refinements in surgical technique may be looked to in the hope of reducing this figure.

SUMMARY

The use of gelatin film for repairing 30 dural defects remaining after excision of meningiomas is reported.

The rate of healing of the wounds and the incidence of continued epilepsy in these 30 cases are contrasted with the results in a similar series of 30 cases where tantalum foil was used to close the dural defect.

No untoward effects were observed in the gelatin series. 6 cases in the tantalum series required further operation for removal of the foil, 3 patients also losing the bone flap from low-grade osteomyelitis.

Comparison of this series with that of Cushing and Eisenhardt (1938) suggests that the closure of dural

TABLE V—INCIDENCE OF PREOPERATIVE EPILEPSY IN PARASAGITTAL AND CONVEXITY MENINGIOMAS

Site	Cushing and Eisenhardt (1938)				Present series			
	Total	Type of epilepsy			Total	Type of epilepsy		
		Preop.	Recurrent	Acquired		Preop.	Recurrent	Acquired
Parasagittal ..	65	34 (*52%*)	30 (*65%*)	13 (*27%*)	21	12 (*57%*)	13 (*46%*)	2 (*18%*)
Convexity ..	29	12 (*41%*)			30	16 (*53%*)		
Total ..	94	46 (*49%*)			51	28 (*55%*)		

lefects with tantalum or with gelatin film leads to a ower incidence of continued epilepsy.

REFERENCES

Busch, E., Bing, J., Hansen, E. H. (1949) *Acta chir. scand.* 97, 410; abstr. *J. Amer. med. Ass.* 140, 1302.
Cushing, H., Eisenhardt, L. (1938) Meningiomas. Springfield, Ill.
Weisel, W., Ross, W. B., Lubitz, J. M., Wood, Wis. (1950) *Arch. Surg.* 60, 87.

XERODERMA PIGMENTOSUM

AN ATTEMPT AT CANCER PROPHYLAXIS

D. W. SMITHERS
M.D. Camb., F.R.C.P., D.M.R.
DIRECTOR OF THE RADIOTHERAPY DEPARTMENT, THE ROYAL CANCER HOSPITAL, LONDON

J. H. WOOD
M.P.S.
CHIEF PHARMACIST, THE ROYAL CANCER HOSPITAL

IN November, 1946, an 8-year-old schoolgirl was sent to us by Mr. Alan Small. She was suffering from xeroderma pigmentosum and had developed a small squamous-cell carcinoma on the vermilion border of her upper lip (fig. 1). Her mother and father were first cousins; her brother, two years older than herself, was moderately freckled. An account of the family has already been published (Koller 1948).

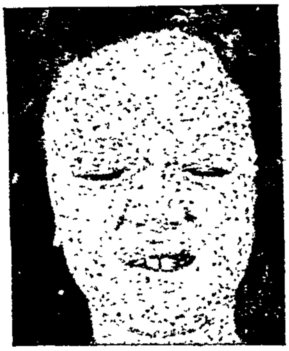


Fig. 1—Patient with xeroderma pigmentosum and a squamous-cell carcinoma of the upper lip before treatment in November, 1946.

This child when we first saw her was wearing long black stockings covering her knees, long black gloves over her arms, and a large black hat. Her parents had been given a most gloomy prognosis by dermatologists, who had warned them that she must always be kept out of the sunlight and should not go out of doors at all during the middle part of the day in summer. The problem presented was the comparatively simple one of dealing with a small early malignant tumour, and the much more difficult one of calming agitated parents and trying to arrange a more normal life for the child.

The tumour of the lip was treated with low-voltage X rays in December, 1946, and has shown no sign of recurrence in the subsequent five years.

An attempt was then made to find the best way of protecting her skin from further damage by sunlight, while a close watch was kept to see that any further tumour that developed as a result of the damage already done would be treated immediately. We studied the literature on the protection of the skin from sunlight and wrote to a number of organisations for advice, receiving helpful suggestions from several sources, including the American Naval Medical Research Institute through the American Embassy and the Medical Research Council.

A PROTECTIVE CREAM

We laid down the following requirements for any preparation to be used for our purpose:

(1) Good screening power.
(2) Easy to apply.
(3) Good covering power.
(4) Moderately water-resistant.
(5) Allow, but not be removed by, perspiration.
(6) Not easily rubbed off but not too difficult to remove.
(7) A finish which would be cosmetically acceptable.

Skin sunburn is due to a comparatively narrow band of wave-lengths in the ultraviolet spectrum. Hausser and Vahle (1922) found a maximum effect at a wave-length of 2975 A°, dropping off to almost no erythema at 2800 A° on one side and 3130 A° on the other. A second region producing erythema less efficiently was found with a maximum at 2540 A°. There is no reliable information about the range of wave-lengths to which the skin is particularly sensitive in xeroderma pigmentosum, but some suggestion that those longer than 3000 A° might be the most important (Zoon 1938). If xeroderma pigmentosum is caused by one of the known "sensitisers" to light, and if this is a hæmatoporphyrin, wave-lengths even longer than 4000 A° might be important. In the absence of information on this point it was necessary to provide for protection over as wide a range of wave-lengths as possible.

The substance with the best covering power was titanium dioxide, and after our first tests with skin partly covered with various preparations and then exposed to ultraviolet light it was decided to use this substance in the final covering cream. Most of the creams tested fell short of our requirements in one or more particulars, the best being one of those advocated by Giese and Wells (1946), in a restricted report made in 1943 to the committee on medical research of the Office of Scientific Research and Development which we were privileged to see and which was published three years later. This cream included titanium dioxide as its mechanical screening and light-dispersing ingredient, and magnesium stearate and butyl stearate for their water-resisting and adhesive properties. Menthyl salicylate was included as an absorber screen to act as some defence in case the continuous phase of the mechanical screen should crack. The vanishing-cream base consisted of stearic acid, cetyl alcohol, and triethanolamine, and the pigment base was made with various salts of iron. The resulting product fulfilled all

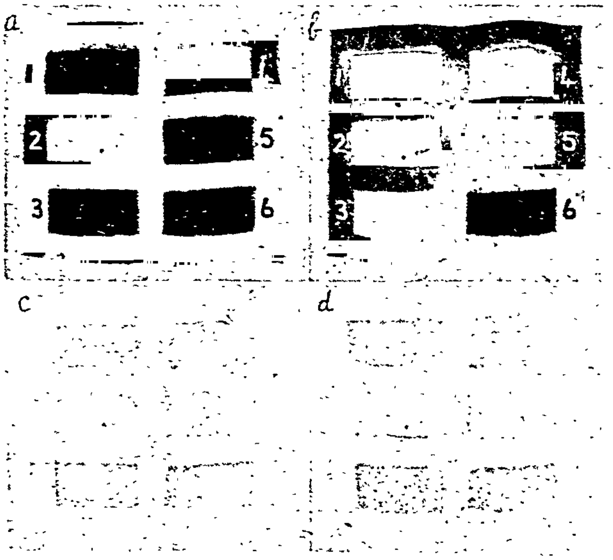


Fig. 2—Skin test. *a*, Protective cut-out; *b*, Protective cut-out after application of creams. *c*, Skin 6 hours after 3 minutes' exposure to ultraviolet light from biosol mercury-vapour lamp 18 in. away. *d*, Same skin 24 hours after exposure.

KEY: (1) Officially issued protective cream.
(2) Royal Cancer Hospital cream prepared in pharmaceutical department.
(3) Control.
(4) Tannic acid 5% in vanishing-cream base.
(5) Elizabeth Arden modification of Royal Cancer Hospital cream.
(6) A proprietary sunburn cream.

our requirements except the last but had a fairly matt appearance.

The cream gave good protection, judged by the amount of erythema produced on exposure to ultraviolet light, spread easily in a thin even layer, stayed on well when placed under a stream of hot or cold water while being stroked with the finger-tips, and came off well when wiped with a detergent before being washed with soap and water. The detailed formula of the cream we made and first used for the child is as follows:

Cream	
Titanium dioxide	25·0%
Magnesium stearate	12·5%
Butyl stearate	12·5%
Menthyl salicylate	20·0%
Pigment base	2·0%
Vanishing cream	28·0%
Pigment Base	
Burnt umber	50%
Red ferric oxide	25%
Yellow ferric oxide	25%
Vanishing Cream	
Stearic acid	15·0%
Cetyl alcohol	1·0%
Triethanolamine	1·5%
Diethyleneglycol mono-ethylether	10·0%
Distilled water	72·5%

To improve the cosmetic appearance which we thought so important in a young girl, who would always have to have her face, neck, arms, and hands covered and her legs as well at times, we appealed to the research department of Elizabeth Arden Ltd. We supplied them with some of our cream and the formula, and they took a great deal of time and trouble in producing a cream which has proved to be most satisfactory for our purpose and most acceptable to the patient.

TESTS

This cream has now been tested by exposing the arms and backs of several persons to the radiation from a 'Biosol' mercury-vapour lamp. Owing to our lack of knowledge of the physical conditions of the creams when applied to the skin, particularly the thickness of the layer, spectral-absorption measurements could not be expected to give very precise information. They did show, however, that thicknesses of about 0·01 mm. were effective in cutting down the radiation by more than 30 times from the shortest ultraviolet wave-length likely to be of any importance up to 5000 A°. The final patch tests were made on volunteers with fair and dark skins, six adjacent skin areas of the same size being exposed to the biosol lamp at a distance of 18 in. for three minutes, which gave a third-degree erythema on the unprotected skin. The six skin areas (fig. 2) were covered as follows: (1) a "protective" cream issued by an official body; (2) the cream prepared by us, the formula of which is given above; (3) a control area of uncovered skin; (4) a cream advocated recently by Russell and Anderson (1950); (5) the Elizabeth Arden modification of the cream used on area 2; and (6) a proprietary sunburn cream.

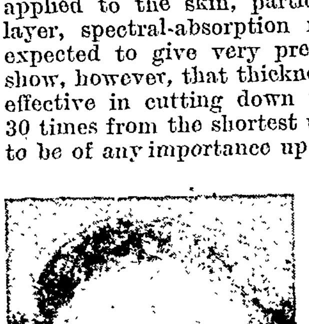


Fig. 3—Patient with xeroderma pigmentosum in July, 1951, with cream and face-powder applied.

Elizabeth Arden Ltd., having produced the cream in a tint most suitable for the child (fig. 3) and taught her to apply it and add an appropriate face-powder, now make the covering cream in three standard shades (light, medium, and dark), which may be had from them at 25, Old Bond Street, London, W.1. Their formula is similar to ours but contains 2% of iso-butyl-para-amino benzoate (Rothman and Rubin 1942) as the sun-screen, and various oxides of iron for colour. The pigmentation is so intense and the covering-power so good that we are now using these creams not only for protecting skin from the effect of sunlight but also as a means of covering scars and other skin blemishes.

Our original patient has worn the cream (fig. 3) on all exposed parts continuously through four summers, which included the particularly sunny summer of 1948, and has led a normal life for a girl of her age, joining in school sports and outdoor pursuits. She has had one further small squamous-cell tumour on the tip of her nose treated without visible scarring during 1951, but is otherwise well and developing normally and cheerfully. The cream has been prescribed for another patient with multiple superficial basal-cell carcinomas of the exposed parts of her skin, and might be useful for patients with solar dermatitis.

We are primarily indebted to the work of Giese and Wells (1946) for the basis on which this cream was developed, and to Mrs. J. Edmunds and Mr. H. W. Avis, of Elizabeth Arden Ltd., who brought it to a satisfactory conclusion. Dr. L. F. Lamerton and Mr. B. M. Wheatley, of the physics department of the Royal Cancer Hospital, assisted us with the skin tests and made the spectral-absorption measurements. Miss J. Hunt and her staff in the department of medical photography not only took many photographs of reactions in black and white, and colour, but also acted as volunteers for exposure to ultraviolet light, sustaining some unpleasant reactions.

REFERENCES

Giese, A. C., Wells, J. M. (1946) *J. Amer. pharmaceut. Ass.* 35, 208.
Hausser, K. W., Vahle, W. (1922) *Strahlentherapie*, 13, 41.
Koller, P. C. (1948) *Brit. J. Cancer*, 2, 149.
Rothman, S., Rubin, J. (1942) *J. invest. Derm.* 5, 445.
Russell, B., Anderson, D. (1950) *Lancet*, ii, 247.
Zoon, J. J. (1938) *Strahlentherapie*, 61, 640.

PSYCHIATRIC FINDINGS IN CROHN'S DISEASE

R. W. CROCKET
M.B. Glasg., F.R.F.P.S., M.R.C.P.E., D.P.M.
SENIOR REGISTRAR AND TUTOR IN PSYCHIATRY, GENERAL INFIRMARY, LEEDS

IN a review of 32 cases of regional ileitis at the General Infirmary at Leeds, Armitage and Wilson (1950) were impressed by the number of patients in whom neurotic traits were prominent. Since the problem of assessment concerned both the departments of surgery and of psychiatry, the assistance of the latter was sought: and the investigation now reported arose on this coöperative basis.

PREVIOUS EVIDENCE

Physiological and experimental evidence for the existence of changes in the colon in response to emotional situations has been growing steadily (Lium 1939, Almy et al. 1949, Grace et al. 1949, 1950). Moreover, clinical observation also has led more than once to the suggestion of a psychoneurotic relationship in this condition.

Bockus (1945), for example, comments on the absence of calm phlegmatic persons with Crohn's disease, and finds anxiety and emotional immaturity to be even commoner in Crohn's disease than in ulcerative colitis. Of 19 patients he found at least 4 who were severely psychoneurotic, 2 of them having been treated as such for a year or more.

Blackburn et al. (1939) reported similar findings, 4 of their patients having been referred to psychiatrists for treatment; but for these workers this indicated simulation of a psychoneurosis by secondary manifestations of long debilitating illness rather than evidence of an ætiological emotional factor.

Crohn's (1949) comment, in connection with social status, race, religion, and nationality as possible factors, is as follows:

"It is unlikely that any of these social factors play a rôle in the ætiological incidence of the disease. . . . My own observations do not impress me with the fact that the ileitis case is much different from a control group of the population. True, many of them are high-strung and anxious: in several instances the patient had been institutionalised for psychoneuroses or anxiety state, the diarrhœa having been completely overlooked. . . .

"The personality of the ileitis case is more stable than that of the patient suffering from ulcerative colitis or peptic ulcer. He has less of the psychosomatic factors so evident in both these latter groups. However, the number of cases of ileitis that have been rescued from institutions for the treatment of mental disease emphasises not the personality but the end-results of the drain of the disease upon the psychic constitution of the sufferer."

Of the clinical features Crohn (1949) wrote:

"The nervous, or rather, the psychic manifestations of this disease are sometimes so manifest that they overwhelm the true somatic manifestations. . . . The evident psychic and nervous symptoms that accompany ileitis often lead to delayed recognition of the true causes of the symptoms. . . . .

"However, ileitis can hardly be classed as a psychosomatic disease; occurrences or recurrences do not follow upon psychic shock as evidently as they can be observed in ulcerative colitis, with obvious relationship of cause to effect."

ANALOGY WITH ULCERATIVE COLITIS

A clinical analogy can be drawn between ileitis and ulcerative colitis.

The evidence for an emotional factor in the latter is strong (Cullinan 1938, Wittkower 1938), but some workers deny this—e.g., Sloan et al. (1950) in a review of 2000 cases. The suggestion is, however, that in Crohn's disease, as in colitis, there may be "an overactive response to an infection, and that its course is determined by emotional and other factors that differ from case to case" (*Lancet* 1948).

The chief advocate of this view is Paulley (1948, 1949), who mentioned 11 cases of Crohn's disease in each of which he found the same personality traits as in 99 of 100 cases of chronic ulcerative colitis, as against 5 of 86 control cases. These traits were "complete dependence, emotional immaturity, lack of normal adult expression, complete lack of aggression, deep narcissism, extreme sensitivity, and an invariable tendency to brood or sulk for long periods over real or imagined wrongs or insults." Paulley suggested that the changes in Crohn's disease might be entirely brought about by chronic intestinal dysfunction, with associated hyperæmia, mucosal lymphœdema, motor irritability, and chronic inflammation, presumably of emotional origin. Secondary agents, such as a virus and the tubercle bacillus, might also be involved. He cited the mucosal states seen on gastroscopy or at operation in cases of duodenal ulcer, and the sigmoidoscopic findings in colon neurosis and colitis, as the type of change envisaged. Paulley (1950) has expanded his description of the personality traits which he finds in ulcerative colitis, and, by inference, in Crohn's disease.

In cases of ulcerative colitis Wittkower (1938) found no uniform personality type; and Mahoney et al. (1949) also failed to uncover any specific personality traits, although they concluded that patients with ulcerative colitis are usually complex neurotics, giving histories of major disturbances in parent-child relationships or of similar childhood traumatic experience.

PRESENT INVESTIGATION

The occurrence of colonic changes in relation to emotion does not constitute an ætiological factor. Something more must be demonstrated. It might be shown, for example, that such changes in the past have been excessive in patients with Crohn's disease. This provides one point of inquiry. Another might lie in the frequency and degree of exposure to emotional stress. A third is in recognition of a relationship between emotional stress and symptoms. In Crohn's disease *in its earliest stages* pain and diarrhœa are usually present, and both may continue intermittently for a long time before a diagnosis is made. One might therefore inquire whether these symptoms have been brought on or exacerbated by emotional stress. This, it should be remembered, is one of the main reasons for general acceptance of the psychosomatic nature of ulcerative colitis. Finally, one may look for the specific personality traits which, it has been suggested, may be associated with Crohn's disease and are presumed to dictate the quality or the quantity of the changes in the gut under emotional stress.

In the present investigation not all the original cases were available for examination, for reasons such as incapacity or distance, but in the outcome 16 patients attended. Each was given a routine diagnostic psychiatric examination lasting about an hour and following up as far as possible any clues uncovered during examination. An attempt was made to formulate short impressionistic summaries which would convey the opinions formed at the time of interview. Special attention was paid to two phases in the course of the disease—the time of onset of symptoms, and the relationship of emotion or stress to symptoms, both before and after operation, which had been done in all the cases.

CASE SUMMARIES

Case 1.—A neatly and tidily dressed married woman, aged 32, heavily perfumed. Not particularly obsessional in personality, but with a record of well-marked childhood neurotic traits. She is shy, retiring, and subject to occasional attacks of acute anxiety. She is also liable to depressive mood swings. Good average intelligence. There is a clear relationship in the history she gives between anxiety and attacks of diarrhœa.

Case 2.—An intelligent man, aged 40, of definite obsessional make-up, but without early neurotic traits apart from this. He is well adjusted to life at home, to his work, and to the fact of his illness. His stresses and anxieties, and the somatic manifestations of the latter, seem to be within physiological limits. There is no correlation between emotional stress and signs and symptoms.

Case 3.—A querulous complaining married woman, aged 44, of good intelligence. She is slightly obsessional, and there is other evidence of psychoneurosis in her personality. She reacts sharply to her not very satisfying marriage, and there is a lingering effect from the emotional trauma of a first love affair. Postoperatively, but not preoperatively, there has been a clear relationship between emotional stress (fear and anger) and subjective symptoms in the stomach.

Case 4.—A young man, aged 27, with a hesitant diffident manner. He seems to have had a good upbringing, with a satisfactory personal background, although to some extent protected. Apart from fear of the dark there is no record of gross childhood anxiety. He is mildly obsessional. His record in the R.A.F. is good. He is mature in his outlook, and has made a satisfactory and realistic adjustment since his operation. The conclusion at interview was that emotional tension did not seem to be a major ætiological factor, although there was a possibility that it might have been a precipitating element. One notes subjective attacks of restlessness and pruritus after operation, as well as the onset of diarrhœa in relation to emotion.

Case 5.—A not very bright spinster, aged 49, with an excellent work record, having settled down in one firm for many years. She is an unmarried mother, and has successfully brought up a son, now aged 22. There is a definite record of anxiety in the past, both childhood and adult: but during the early stages of her ileitis severe emotional stress caused by the sudden death of her son's father, who had been supporting her financially, did not affect her symptoms in any way. She has been perfectly well for the past nine years.

Case 6.—A happily married woman, aged 37, of average intelligence, with four children. There is a grossly neurotic family background, and she is highly neurotic, with, however, some adjustment on the basis of character and personality traits. There have been depressive swings in relation to her illness and operations, and a definite connection between emotional state and symptoms.

Case 7.—A quick intelligent married woman, aged 45, highly neurotic, with excellent insight and considerable

PSYCHOLOGICAL FINDINGS IN CROHN'S DISEASE

	Case no.															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
History of previous "emotional" diarrhœa	+							+					+			
Chronic adult anxiety traits	+	0	+	0	+	+	+	+	+	+	+	0	0	0	0/+	0
Childhood anxiety traits	+	0	+	0/+	+	+	+	+	+	+	0	0	0/+	0/+	0	0
Obsessional traits		+	+				+			+			+		+	
Obsessional traits at times disabling (all mildly so) ..			+				+			+						
Misdiagnosed "nerves" at some stage			+			+			+	+						
Subjective preoperative relationship of emotion to symptoms	+	0	0	0	0	+	0	0	0	0	0	0	0	0	+	0
Subjective postoperative relationship of emotion to symptoms	0	0	+	+	0	0	0	0	0	0	0	0	0	0	+	0

adjustment. She is emphatic that emotion has no real connection with her symptoms. She shows numerous mildly obsessional traits, but they are just within physiological limits. She feels a necessity to "control" herself in emotional situations, but usually without success.

Case 8.—A married woman, aged 34, with definite neurotic tendencies and a similar family background. Emotional changes have had no effect on her symptoms of diarrhœa, nausea, sickness, and pain, even though all her life she has been accustomed to going to the lavatory before going "anywhere special," to minimise feelings of tension and nervous diarrhœa. Onset of Crohn's disease came six months after marriage, but there is no evidence of special stress in relation to this. There was perversion of appetite at the time of onset. This is a patient who would have benefited decidedly from psychotherapeutic reassurance and assistance throughout her illness.

Case 9.—A small, irascible, and somewhat brusque little man, aged 47, originally diagnosed as having colitis. There is a definite neurotic element in his make-up, to which he is, however, well adjusted. There is evidence of slight but definite anxiety in childhood, but no gross affective changes in the past. There is no subjective relationship of symptoms to emotion, and no relationship of emotional disturbance to onset of Crohn's disease, in spite of substantial intermittent emotional stress. (This patient's memory was notably bad.)

Case 10.—A married woman, aged 69, with a highly neurotic record. The onset of her illness was associated with severe affective disturbance, but symptoms were not related to emotional tension or stress. She still has residual affective illness, but is reasonably well adjusted.

Case 11.—A married woman, aged 32, mildly predisposed to neurosis, with episodic emotional outbursts as part of her ordinary personality make-up, highly strung, and quick-tempered. She is at present well adjusted, and is happily married, with good domestic arrangements. No definite psychological factors associated with the onset of her illness, although preoccupation with cancer of the bowel in a friend led to association of her early symptoms with the idea of cancer, with morbid anxiety as a result. There has been no subjective relationship between emotional tension and symptoms.

Case 12.—A man, aged 38, obviously very ill. Not very bright intellectually. No record of neurosis in early life, and as an adult he seems to have been an active person, with a well-adjusted premorbid personality. Signs and symptoms have been unrelated to emotional stress; nor is there any record of stress at onset. His symptoms, when established, exacerbated some domestic difficulties with his wife, who left him as a result eight years ago.

Case 13.—A thin extroverted married woman, aged 30, bright, quick, and with some highly developed obsessional traits. Her feelings are readily reflected in her behaviour. She is well adjusted emotionally so far as childhood anxiety traits are concerned, but about puberty she experienced an episode of "nervous" diarrhœa in relation to an examination. No apparent connection between emotion and onset of Crohn's disease, and no recognised relationship of emotion to symptoms.

Case 14.—A quiet married woman, aged 27, with a wel adjusted personality. There is a record of mild childhoo anxiety only. No relationship between emotion and symptom or between emotional stress and onset of Crohn's disease She was depressed for six months before her illness, and sh has had much domestic and marital upset since her operation Her husband might be described as "mother-fixated." Since her operation her disposition has changed, in that she easily gets into a temper in a way that she did not before.

Case 15.—A tall thin man, aged 57, who used to be stout He is somewhat aggressive, methodical, and systematic, wit a stable and steady outlook at work. No record of anxiet in childhood, but for many years he has had a choking reactio to emotional stress—e.g., at the cinema during exciting scenes and when angry—but no bowel effect before his illness. Sinc its onset, however, he has noticed a definite connectio between attacks of diarrhœa and emotion. This is no greate since his operation than before, but he is much more irritabl since the operation. No evidence of an emotional factor i the origin of his Crohn's disease.

Case 16.—An active man, aged 33, of average intelligence without any evidence of neurotic disability, happily married and a good workman. No emotional origin found for hi illness, and no relationship discerned between emotion and symptoms. He seems never to have had substantial somatic emotional tension.

RESULTS

The findings in the cases are summarised in the accompanying table. In 3 of the 16 patients anxiety had at some time or other been associated with diarrhœa sufficiently to be remembered beyond doubt. In cases 1 and 13 this was at the age of 12 years in connection with scholarship examinations; in case 8 it was a regular occurrence at times of stress all her life, so much so that she regularly anticipated necessity by going to the lavatory before any special occasion. It is very doubtful if the occurrence of 3 cases of this kind has any significance. 9 patients showed chronic adult anxiety traits, and 8 of them had a history of childhood anxiety. At first sight this might be taken as strongly suggesting an ætiological factor. There is considerable evidence, however, that this is in keeping with the general incidence of chronic anxiety in comparable groups of patients without either Crohn's disease or ulcerative colitis. In 25 unselected patients in a general hospital ward, for example, examined in a way very similar to the present group, only 6 had no psychiatric abnormality bearing on symptoms; and this sort of result has been previously obtained with much larger series of both inpatients and outpatients (Moersch 1932, Dunbar 1943, Pemberton 1951). Although the present group may certainly be considered heavily "loaded" with psychoneurotic illness, it is not sufficient to carry any definite ætiological significance.

Only 5 of the 16 patients recognised subjectively a relationship between emotional stress and the symptoms of Crohn's disease, and 2 of these did so only after operation, which involved resection in 4 and laparotomy in 1 (case 15). This was so despite precise and persistent questioning in all cases.

Examination was limited to one psychiatric interview, and assessment of personality was therefore impressionistic. No definite evidence of a characteristic Crohn's disease personality emerged. In particular, dependency as a personality trait did not appear to be unduly prominent; nor was immaturity particularly noticeable. Obsessional traits, traditionally related in psychopathology to preoccupation with bowel function, were obvious in 6 patients, but in only 3 did they cause any conscious distress, and in these cases it was slight.

There come to mind, in dealing with such patients, questions which are not readily answered by the technique of examination used here. For example, is it possible that insidious changes in the intestines in relation to emotion may take place in a chronic way, without manifestations in response to, or in association with, acute subjective emotional experience? If so, then psychiatric interviewing alone is unlikely ever to provide sufficient relevant evidence. Again, it is an everyday psychological observation that subjective emotional tension resulting from a particular environmental stress may diminish, even though the stress continues. Processes such as repression, dissociation, and compulsive obsessional preoccupation may be clearly recognisable on these occasions. Is it possible that such mental mechanisms can dispose of the conscious component of fear, anger, or anxiety, and the somatic changes still occur? That this may be so is supported by such evidence as Golla's (1921) finding that electrical skin resistance falls with noxious stimulation, not only on the first occasion but also with repetition, after the patient has become accustomed to it and is no longer subjectively aware of any stress.

CONCLUSION

Other techniques of investigation may help with such questions. So far as the present review is concerned, routine psychiatric examination does not give substantial support for the suggestion that emotional stress is a major ætiological factor in Crohn's disease. Such examination does confirm, however, that in some patients emotional stress plays a material part in the formation of symptoms; and in this sense may be accepted as a factor capable of affecting the course of the illness, although ordinarily within physiological expectation.

I wish to thank Mr. George Armitage for putting these patients at my disposal; and Mr. Michael Wilson, Prof. D. R. MacCalman, and Dr. W. Ironside for encouragement and advice.

REFERENCES

Almy, P. A., Kern, F. jun., Tulin, M. (1949) *Gastroenterology*, 12, 425.
Armitage, G., Wilson, M. (1950) *Brit. J. Surg.* 38, 182.
Blackburn, G., Hadfield, G., Hunt, A. H. (1939) *St. Bart's Hosp. Rep.* 72, 181.
Bockus, H. L. (1945) *J. Amer. med. Ass.* 127, 449.
Cullinan, E. R. (1938) *Brit. med. J.* ii, 1351.
Crohn, B. B. (1949) Regional Ileitis. London.
Dunbar, F. (1943) Psychosomatic Diagnosis. London.
Golla, F. L. (1921) *Lancet*, ii, 215.
Grace, W. J., Seton, P. H., Wolf, S., Wolff, H. G. (1949) *Amer. J. med. Sci.* 217, 241.
— Wolf, S., Wolff, H. G. (1950) *J. Amer. med. Ass.* 142, 1044.
Lancet (1948) i, 835.
Lium, R. (1939) *Arch. intern. Med.* 63, 210.
Mahoney, V. P., Bockus, H. L., Ingram, M., Hundley, J. W., Yaskin, J. C. (1949) *Gastroenterology*, 13, 547.
Moersch, F. P. (1932) *Amer. J. Psychiat.* 11, 831.
Paulley, J. W. (1948) *Lancet*, i, 923.
— (1949) *Proc. R. Soc. Med.* 42, 241.
— (1950) *Gastroenterology*, 16, 566.
Pemberton, J. (1951) *Lancet*, i, 224.
Sloan, W. P. jun., Bargen, J. A., Gage, R. P. (1950) *Gastroenterology*, 16, 25.
Wittkower, E. (1938) *Brit. med. J.* ii, 1356.

BRAIDED TANTALUM WIRE

JOHN HOWKINS
M.D., M.S. Lond., F.R.C.S., F.R.C.O.G.
ASSISTANT GYNÆCOLOGICAL SURGEON, ST. BARTHOLOMEW'S HOSPITAL; GYNÆCOLOGICAL SURGEON, ROYAL MASONIC HOSPITAL AND HAMPSTEAD GENERAL HOSPITAL, LONDON

S. F. HANS
M.D. Lond., M.R.C.O.G.
CLINICAL ASSISTANT TO HAMPSTEAD GENERAL HOSPITAL AND ST. JOHN'S HOSPITAL, LEWISHAM

STAINLESS steel wire has now been used for the closure of abdominal incisions long enough to justify the statement that it is a satisfactory suture. Of all sutures it probably causes the least cellular reaction and gives the soundest and least troublesome healing. Having been introduced to its use by Mr. Alan Hunt in 1946 one of us (J. H.) has employed it consistently in all abdominal operations without any regrets ever since that time. It has, however, one small and irritating disadvantage—it is liable to kink and then to break. Because of this disadvantage we tried braided tantalum wire (gauge 0), which, being more flexible, is not subject to kinking. As a suture braided tantalum wire is as easy to use as catgut and at first sight appears to be an advance on stainless steel. It was employed at four hospitals for some months in 1950 until it was realised that it had certain considerable disadvantages. The purpose of this short communication is to warn surgeons against the use of braided tantalum as a suture.

Soon after the introduction of braided tantalum a number of patients were seen at postoperative examination with persistent sinuses and stitch abscesses. Some of these required exploration of their wounds and the removal of the tantalum before these sinuses closed. Later postoperative examinations revealed that the healing of some abdominal wounds was not sound, and in some patients herniæ had developed in the incisions. It was therefore decided to review the cases in which braided tantalum had been used in two hospitals and this random sample is submitted for examination (see table).

Cases in which a midline subumbilical incision was closed with a continuous suture of gauge-O braided tantalum wire

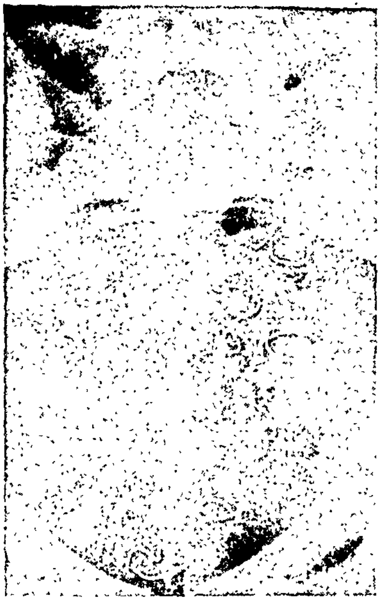
Total number	136
Herniation of scar	9
Sepsis in scar	11
Removal of wire necessary	6 (of the above 11)

It will be seen that of the 136 patients who were examined 9 had small herniæ, 1 of which required a subsequent repair. Abscesses and sinuses had been troublesome in 11 patients, in 6 of whom it was necessary to remove the tantalum wire before they healed. These 11 patients all eventually healed satisfactorily, including 1 in whom the sinus was probably tuberculous. Such a state of affairs cannot be described as satisfactory, and the use of tantalum was immediately abandoned and a retreat was made to 35-gauge stainless steel wire.

In many hundreds of cases in five years in which stainless steel wire has been used we can only remember 2 cases in which sinuses formed and it was necessary to remove the wire, and no cases of postoperative herniation have been seen. It should, however, be pointed out that we have not reviewed all the cases in which stainless steel wire was used, and that this is merely a clinical impression from the outpatient follow-up of cases. It is always possible that postoperative troubles have been dealt with at other hospitals unknown to the original operator. The fact, however, that they have not been seen at the hospital where the operation was performed is presumptive evidence that the number has been inconsiderable. Abel and Hunt (1948), in a far larger series than ours, emphasise the rarity of postoperative troubles. In 2500 laparotomies they report no incisional hernia and no disruption of the wound.

These workers refer to tantalum wire and note that "it is easier to use than stainless steel and has less tendency to kink. It is, however, not so strong and more brittle in the knot" (Abel and Hunt 1948). With all these statements we agree.

The accompanying illustration is from a case in which incisional hernia was repaired with continuous and interrupted sutures of braided tantalum wire. It illustrates the brittleness of tantalum and suggests the genesis of incisional hernia where this suture is used. It should be noted that the interrupted as well as the continuous sutures have broken. Douglas (1949) has made extensive tests of the relative tensile strengths of the various suture materials both in the laboratory and in living tissue. His figures show that tantalum has roughly half the tensile strength of stainless steel.



Fragmentation of tantalum-wire sutures.

CONCLUSIONS

Braided tantalum wire (gauge 0) has not the tensile strength of a comparable gauge of stainless steel.

Of 136 patients whose abdominal incisions were closed with this wire, 11 developed sepsis in the scar, and in 6 of these cases it was necessary to remove the wire before healing took place.

Incisional hernia developed in 9 of the 136 patients.

REFERENCES

Abel, A. L., Hunt, A. H. (1948) *Brit. med. J.* ii, 379.
Douglas, D. M. (1949) *Lancet*, ii, 497, 499.

INFLUENCE OF ORGANIC PHOSPHATES ON TUBERCULIN SENSITIVITY IN B.C.G. INFECTED GUINEAPIGS

RELATION TO CORTISONE DESENSITISATION

J. W. Cornforth
M.Sc. Sydney, D.Phil. Oxfd

D. A. Long
M.D. Lond.

From the National Institute for Medical Research, Mill Hill, London

A.C.T.H. and cortisone depress, and thyroxine increases, hypersensitivity to tuberculin in guineapigs infected with B.C.G. (Long and Miles 1950). But small amounts of thyroxine are needed for desensitisation by the adrenal hormones, which then depress hypersensitivity to the same final level irrespective of the amount of thyroxine available (Long, Miles, and Perry 1951b). The link between this complex interaction of hormones may lie in the metabolism of ascorbic acid; for it is probable that, in the guineapig, the oxidation of ascorbic acid to dehydroascorbic acid initiates desensitisation, and that the thyroid and adrenal hormones exert their influence on the sulphydryl reducing system responsible for maintaining in the tissues the balance between ascorbic and dehydroascorbic acid (Long, Miles, and Perry 1951a and c, Long 1952). This argument is strengthened by the observation that alloxan, which combines with -SH compounds, diminishes sensitivity to tuberculin and bears the same relation to dietary and hormonal factors as cortisone (fig. 1) (Long et al. 1951a, b, and c); and also by the fact that the injection of th -SH compound glutathione prevents desensitisation by cortisone (Long et al. 1951c).

In vitro, alloxan inhibits the conversion of glucose-1-phosphate (Cori ester) to glucose-6-phosphate (Robinso ester), the second step in the metabolism of glycoge This inhibition is attributed to its action as an enzym destroyer (Lehmann 1939). Alloxan, which has in an case a very short life in the body (Archibald 1945 may not itself exert this influence on the enzyme in viv but may do so by inducing overproduction of dehydro-ascorbic acid, which has already been inferred to be th more immediate agent in alloxan desensitisation (Lon et al. 1951c) and which has a chemical structure simila to alloxan. If, then, these speculations are correct cortisone and alloxan facilitate the formation of dehydro-ascorbic acid which inactivates phosphoglucomutas and so blocks the conversi [illegible] t glucose-6-phosphate, with [illegible] ne (fig. 2). On the assumption that glucose-1-phosphat represents the next step in the chain of metabolic event leading to diminished sensitivity to tuberculin, it was tested for desensitising power and proved active in a dose of less than 0·025 mg. per kg. body-weight, which is many times less than the minimum effective dose o cortisone, alloxan, or dehydroascorbic acid. Glucose-1-phosphate is of course normally present in the body, but its presence has not to our knowledge been reported in extracellular fluids in vivo. This may account for th effect observed on injection of a dose which must b quite small relative to the body's normal turnove of glucose-1-phosphate. Glucose-6-phosphate, the product formed from glucose-1-phosphate by phosphoglucomutase was also found to desensitise, but the dose required is several hundred times larger than the effectiv dose of glucose-1-phosphate. This effect may perhaps be due to the equilibrium glucose-1-phosphate ⇌ glucose-6-phosphate, a large excess of the latter component producing a smaller excess of the former.

In the present paper, the effect on tuberculin sensitivity of glucose-1-phosphate and of other biologically significant phosphorus compounds is compared with that of other desensitising agents—namely, cortisone, alloxan, ascorbic acid and its metabolites (Long 1952), N-acetylsphingosine (Fisher, Harington, and Long 1951), and certain phenolic polyoxyethylene ethers (D'Arcy Hart, Long, and Rees 1952). In addition, the observation that lysergic acid diethylamide, an amide of one of the constituents of ergot, increases, in very small oral doses, the level of hexosemonophosphate in the blood of man, apparently by blocking its further enzymatic breakdown (Mayer-Gross, McAdam, and Walker 1951), provided a second method for testing our hypothesis, since if our speculations are correct, this drug should cause a diminution in sensitivity to tuberculin. It did so, in a dose of less than 0·0002 mg. per kg.

METHODS AND RESULTS

350 g. albino guineapigs of the Hampstead strain, fed upon a pelleted diet (Bruce and Parkes 1947), supplemented with unlimited cabbage, were injected with B.C.G. vaccine, and sensitivity to tuberculin was estimated by the method of Long and Miles (1950). All drugs tested, with the exception of glutathione, N-acetylsphingosine, and cortisone acetate, were dissolved in 1 ml. of normal saline and injected subcutaneously two hours before the tuberculin.

Phosphates supplied as barium salts were dissolved in saline, treated with a little sodium sulphate, and freed from barium sulphate before injection. Where the substance was given as a salt, the dose has been recalculated to give the amount of organic anion actually present. N-acetyl-sphingosine and cortisone acetate were suspended in 1 ml.

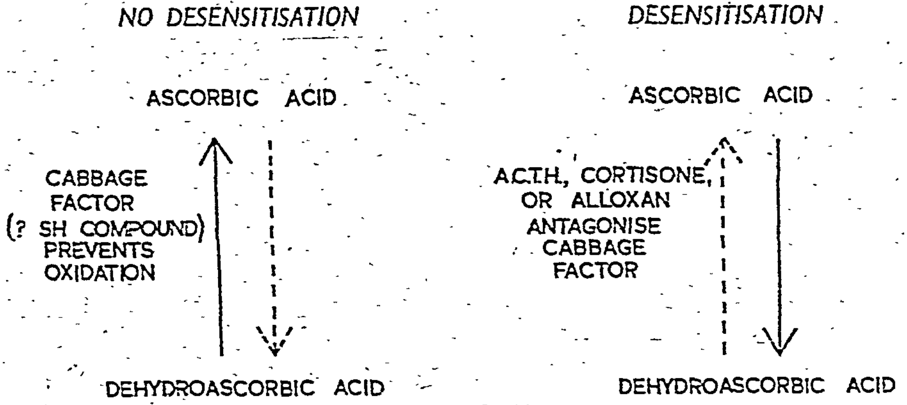

NO DESENSITISATION
ASCORBIC ACID
CABBAGE FACTOR (? SH COMPOUND) PREVENTS OXIDATION
DEHYDROASCORBIC ACID
DESENSITISATION
ASCORBIC ACID
A.C.T.H., CORTISONE, OR ALLOXAN ANTAGONISE CABBAGE FACTOR
DEHYDROASCORBIC ACID

Fig. 1.

of normal saline and injected subcutaneously six hours before the tuberculin. Reduced glutathione was dissolved in gas-free distilled water and adjusted with sodium bicarbonate solution to pH 6; approximately 150 mg. per kg. in a volume of 2 ml. was injected intraperitoneally two hours before the tuberculin.

The dose of a drug depended partly on its availability: some phosphates, inactive in the dose actually given, might at higher dose levels have desensitised.

After preliminary experiments had shown glucose-1-phosphate to be an effective desensitising agent in doses of 0·01 mg. per kg., whereas glucose (100 mg. per kg.) and sodium phosphate (100 mg. per kg.) were without effect, it was decided to test, on an empirical basis, other organic phosphate compounds representing the various stages of phosphorus metabolism. Glucose-6-phosphate, fructose-6-phosphate and fructose-1, 6-diphosphate, though active in a dose of approximately 50 mg. per kg, were inactive at 3 mg. per kg. Fructose-1-phosphate (3 mg. per kg.), phosphopyruvate (2·5 mg. per kg.), phosphoglycerate (2·5 mg. per kg.), riboflavine phosphate (15 mg. per kg.), adenosine triphosphate (12 mg. per kg.), adenosine-5′-phosphate (50 mg. per kg.), and glycerophosphate (50 mg. per kg.) were without significant effect. Ribose-5-phosphate had comparable desensitising power to glucose-1-phosphate, being effective in a dose of 0·04 mg. per kg. Adenosine diphosphate (2·5 mg. per kg.) and adenosine-3′-phosphate (2·5 mg. per kg.) proved effective. Lysergic acid diethylamide, as already stated, diminished sensitivity to tuberculin in a dose of 0·00018 mg. per kg.

According to our hypothesis, the activity of phosphoglucomutase is inhibited by dehydroascorbic acid, with the result that glucose-1-phosphate accumulates and causes a diminution in sensitivity to tuberculin. But reduced glutathione assists the action of phosphoglucomutase (Lehmann 1939), so that dehydroascorbic acid might block phosphorylation by oxidising glutathione rather than by exerting an anti-enzymic effect. If so, the injection of an excess of reduced glutathione should prevent desensitisation by glucose-1-phosphate. It failed to do so (see table), thus supporting the idea that dehydroascorbic acid influences phosphoglucomutase itself. Reduced glutatione prevents desensitisation by cortisone acetate and by ascorbic acid (Long et al. 1951b); this was confirmed and shown also to apply to desensitisation by alloxan and dehydroascorbic acid, but not to desensitisation by glucose-1-phosphate, the phenolic polyoxyethylene ethers or N-acetylsphingosine. This suggests, first that -SH compounds can block the chain of chemical events as far as dehydroascorbic acid, and secondly that N-acetylsphingosine and the polyoxyethylene ethers exert their effect after this stage. They may in fact influence sensitivity by affecting phosphorus metabolism, with which sphingosine is known to be linked, but we have no evidence to support this contention. Neither are we in a position to explain the marked desensitising properties of ribose-5-phosphate or the less marked effects of adenosine diphosphate or adenosine-3′-phosphate. Nevertheless, the independence on dietary and hormonal factors of the action of glucose-1-phosphate, the lack of antagonistic effect exerted by glutathione, the very small effective dose and the confirmatory evidence provided by the desensitising action of lysergic acid diethylamide, suggest to us that glucose-1-phosphate is more directly linked with the sensitivity of tissues to tuberculin than any other substance with which we have experience.

EFFECT OF REDUCED GLUTATHIONE UPON DESENSITISATION BY VARIOUS AGENTS

Agent and dose per kg. body-weight	Desensitisation	
	Glutathione (150 mg. per kg.)	No glutathione
Alloxan (25 mg.)	−	+
Ascorbic acid * (50 mg.)	−	+
Cortisone acetate (5 mg.)	−	+
Dehydroascorbic acid (50 mg.)	−	+
Glucose-1-phosphate (12 mg.)	+	+
N-acetylsphingosine (30 mg.)	+	+
Polyoxyethylene ethers (20 mg.)	+	+

* In pellet-fed guineapigs.

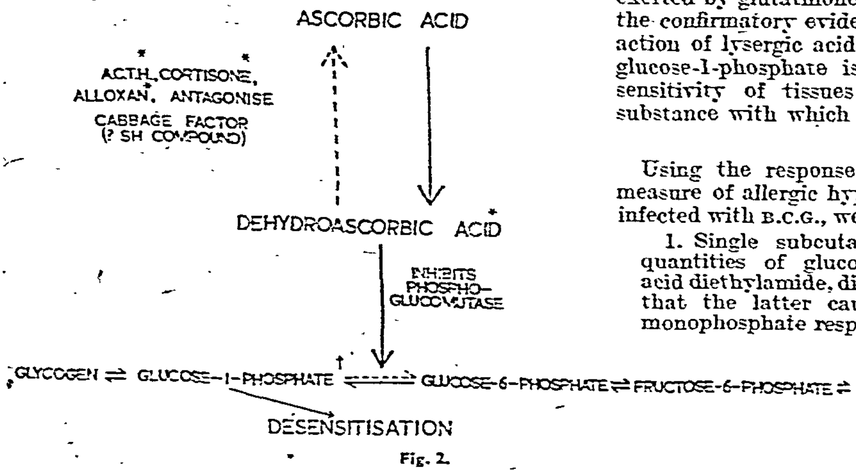

ASCORBIC ACID
* *
A.C.T.H., CORTISONE, ALLOXAN, ANTAGONISE CABBAGE FACTOR (? SH COMPOUND)
DEHYDROASCORBIC ACID *
INHIBITS PHOSPHO-GLUCOMUTASE
GLYCOGEN ⇌ GLUCOSE-1-PHOSPHATE ⇌ GLUCOSE-6-PHOSPHATE ⇌ FRUCTOSE-6-PHOSPHATE ⇌
†
DESENSITISATION

Fig. 2.

* Desensitising action prevented by reduced glutathione.
† Desensitising action not prevented by reduced glutathione.

SUMMARY

Using the response to intradermal tuberculin as a measure of allergic hypersensitivity in albino guineapigs infected with B.C.G., we find that:

1. Single subcutaneous injections of very small quantities of glucose-1-phosphate, and of lysergic acid diethylamide, diminish sensitivity. It is suggested that the latter causes an accumulation of hexose monophosphate responsible for densensitisation.

2. Injected reduced glutathione prevents the desensitising action of cortisone acetate, alloxan, ascorbic acid, and dehydroascorbic acid, but not of glucose-1-phosphate, N-acetylsphingosine and the polyoxyethylene ethers. The

relation of these findings to the mechanism of cortisone desensitisation are discussed.

Our present hypothesis (see fig. 2) provides what we believe to be a useful, though probably oversimplified, summary of the mechanism of cortisone desensitisation. We suggest that cortisone facilitates the oxidation of ascorbic to dehydroascorbic acid. Dehydroascorbic acid inhibits phosphoglucomutase, and as a result glucose-1-phosphate accumulates in the tissues and is intimately concerned with desensitisation.

We are indebted to Dr. Knud Tolderlund, of the State Serum Institute, Copenhagen, for the B.C.G.; to Mr. P. N. Campbell, PH.D., Prof. F. Dickens, F.R.S., Dr. J. D. Judah, Prof. M. Stacey, F.R.S., and Dr. F. Wrigley, of Roche Products Ltd., for phosphate compounds; to Sir Charles Harington, F.R.S., for the N-acetylsphingosine; to Dr. Wrigley, for the glutathione; and to Messrs. Sandoz Ltd., for the lysergic acid diethylamide. We are grateful to our colleagues, Dr. G. Popják for advice on various aspects of phosphorus metabolism and for providing many of the drugs, and to Mr. T. S. Work, PH.D., for drawing our attention to the biochemical effects of lysergic acid diethylamide.

It is a pleasure to acknowledge the help of Dr. W. L. M. Perry and Miss M. V. Mussett in the statistical analyses of the large number of experiments on which these observations are based.

REFERENCES

Archibald, R. M. (1945) *J. biol. Chem.* 158, 347.
Bruce, H. M., Parkes, A. S. (1947) *J. Hyg., Camb.* 45, 70.
Fisher, N., Harington, C. R., Long, D. A. (1951) *Lancet*, ii, 522.
Hart, P. D'Arcy, Long, D. A., Rees, R. J. W. (1952) *Brit. med. J.* i, 680.
Lehmann, H. (1939) *Biochem. J.* 33, 1241.
Long, D. A. (1952) *Bull. Schweiz. Akad. med. Wiss.* 8, 194.
— Miles, A. A. (1950) *Lancet*, i, 492.
— — Perry, W. L. M. (1951a) *Ibid*, i, 1085.
— — — (1951b) *Ibid*, p. 1302.
— — — (1951c) *Ibid*, ii, 902.
Mayer-Gross, W., McAdam, W., Walker, J. W. (1951) *Nature, Lond.* 168, 827.

Reviews of Books

Atlas of General Affections of the Skeleton

Sir THOMAS FAIRBANK, D.S.O., O.B.E., F.R.C.S. Edinburgh:
E. & S. Livingstone. 1951. Pp. 411. 55*s*.

THIS great book is the product of many years' work. Sir Thomas Fairbank's well-known interest in generalised diseases of bone has resulted in a collection of case-histories and radiographs from many parts of the world and is probably unrivalled. The book is therefore authoritative. The diseases have been classified as far as possible according to their ætiology; but, as the causes are in many cases unknown, a true classification is difficult. Nevertheless, the present arrangement makes for easy reference. The best-known names are used for the various conditions, and their originators are listed: three of the conditions have been named by Fairbank himself with general acceptance. The known causes of the various diseases are given; but no effort has been made to discuss rival theories where the cause of a disease is still obscure. The many excellent illustrations and radiographs are well chosen and finely reproduced.

Tumeurs du sein

HENRI HARTMANN, honorary professor of the Faculty of Medicine, Paris. Paris: Masson. 1951. Pp. 103.
Fr. 1200.

Professor Hartmann has collected in a monograph of 100 pages a vast amount of information about tumours of the breast, analysing 142 cases of fibro-adenoma, 238 cases of fibro-adenosis, and 2600 cases of carcinoma, together with a small series of cases of sarcoma and tuberculosis. The analysis of these cases, according to age-incidence, site, and clinical presentation, conforms to series already published elsewhere, and sets out, in small compass, all the essential information available.

Some of the views expressed are at variance with those commonly accepted in this country. Professor Hartmann regards fibro-adenosis as a precancerous lesion, but the arguments which he quotes in support of this are not particularly cogent, depending on a study of 48 uncontrolled cases of cancer of the breast, and on the well-known work of Lacassagne on mice. He shares with British clinicians doubts about the efficacy of hormone treatment in fibro-adenosis, and condemns the injection of sclerosing fluids into cysts. For the doubtful lump he advocates a wedge-shaped resection; but he is more inclined to do a total mastectomy in patients over the age of 40 with fibro-adenosis than are most surgeons here. It is somewhat strange to us, too, to see a serious discussion as to whether there is a relationship between syphilis and cancer of the breast. He quotes figures from Paris clinics showing that 20–40% of cases of cancer of the breast have a positive Wassermann; but, as he shrewdly remarks, "la syphilis est, à Paris, très répandue." He believes that trauma may aggravate pre-existing cancer, but does not think there is any evidence to show that trauma can initiate growth.

The various types of cancer of the breast are well described and conform to the classification accepted in this country. What we now call "Paget's disease" was originally described, as Professor Hartmann shows conclusively, by Nélaton in 1854; but, as if to make up for this blow, he gives to Moore of the Middlesex Hospital credit for originating, as early as 1867, treatment for cancer by removal of the breast with the glands in the axilla and the pectoral muscle together in one block. In Professor Hartmann's own clinic in 827 radical mastectomy operations the mortality was 1·25%, which reflects the excellence of his methods. He recommends that solitary recurrences after radical mastectomy should be removed surgically and he quotes several case-histories to show how satisfactory this measure may be—a view with which most workers in this country would agree.

A final chapter on the serological diagnosis of cancer may disturb the confidence of some readers in the integrity of the rest of the book. This method must, at the very best, be considered to be sub judice, and it seems a pity that a work primarily designed for the instruction of the young surgeon and of the student should advocate a method about which there is much serious doubt.

Surgical Technique

STEPHEN POWER, M.S., F.R.C.S., senior surgeon, Dreadnought Hospital, London. London: Heinemann Medical Books. 1951. Pp. 380. 30*s*.

IT is difficult to appraise this book. It is a collection of hints on those details of surgical craftsmanship which any experienced surgeon carries out almost unconsciously, and it deals with things that cannot be fully learnt except by association with a master. It is an interesting and personal little book, but as a guide to house-surgeons it would be more acceptable if it had been more comprehensive.

The Significance of Heredity in Ophthalmology

A Tasmanian Survey. J. BRUCE HAMILTON, M.D. Sydney, D.O. Oxfd, D.O.M.S., F.R.A.C.S., senior ophthalmic surgeon, Royal Hobart Hospital. Melbourne: A. H. Massina. 1951. Pp. 135. 50*s*.

THIS study is an account of hereditary eye disease seen in Tasmania, a large territory with fewer than a quarter of a million inhabitants in 1933. In this relatively manageable population Bruce Hamilton has made intensive search for the families of persons affected with genetic eye disease.

In eighteen such affections he has been able to construct 114 pedigrees, 31 being on refractive errors, 25 on the different varieties of squint, 10 on glaucoma, and 8 on dacryocystitis. They all bear out the accepted modes of inheritance in these affections. His pedigrees on different varieties of cataract likewise follow the classical pattern. In retinitis pigmentosa there are pedigrees illustrative of both the recessive and the dominant type. Of special interest is his pedigree of retinal detachment associated with cystic changes in the lungs, and of sarcoma in a woman and her niece. Detailed family histories are given, and full references to relevant literature.

An introductory section contains some general principles and some suggestions for eugenic legislation—a subject on which the author appears to be more enthusiastic than most geneticists.

THE LANCET

LONDON: SATURDAY, MAY 10, 1952

Facts about B.C.G.

After the late war an international programme of mass B.C.G. vaccination was initiated by the Joint Enterprise, formed by Unicef, the Danish Red Cross, the Norwegian Relief for Europe, and the Swedish Red Cross. The Tuberculosis Research Office of W.H.O. was established in Copenhagen to study the problems brought to light during the early stages of this vast campaign; and some of the results of investigations during the past two years are described in this issue by Dr. Carroll Palmer, the director. Many have not yet been published, partly because much of the work had to be repeated when the early findings were found to differ so much from what is generally accepted about B.C.G. To supplant traditional beliefs the evidence must be excellent. That brought forward by Dr. Palmer seems to be unassailable; the experiments were carefully planned, methodically executed, and accurately analysed. Had similar experiments been carried out years ago when B.C.G. vaccination was in its infancy, the confusion and controversy that have hampered its development might have been averted.

The tuberculin skin reaction is indispensable in the study and practice of B.C.G. vaccination. Despite its many inherent limitations, it gives a quantitative guide to the tuberculin hypersensitivity of the skin. Until lately, however, very little attention was paid to the accuracy of the test. Meyer et al.[1] have now shown that with experienced testers the experimental error in the observed size of the skin induration has a standard deviation of about 2 mm. Thus, where the diameter of the indurated area is 10 mm., about 30% of tests under these conditions will be recorded as above 12 mm. or below 8 mm. A diameter of 6 mm. is commonly taken as the lower limit of a "positive" reaction; and there may be some support for this convention in Dr. Palmer's evidence that the frequency-distribution of the skin reactions of large numbers of persons to the same dose of tuberculin shows two peaks with between them a region of very low frequency around a diameter of 6 mm. By this definition of a "positive" reaction, Meyer and his colleagues found that 10% of people with a "negative" reaction on one arm had a "positive" reaction on the other. The experimental error with inexperienced testers and between testers of varied skill is likely to be great. Indeed, in the Medical Research Council's tuberculin survey[2] variations between testers were so great that degrees of sensitivity in different parts of the country could not be compared, and it was possible to measure infection only by the total "positives," irrespective of whether a jelly test or an intradermal test was used. This sufficed for the main purpose of this particular survey, but much valuable information was probably lost by the differences in interpretation. For many research purposes the recording of "positive" reactions is insufficient. The W.H.O. workers have measured the level of tuberculin sensitivity in different groups by the mean diameter of the reactions; and in this way they have investigated accurately some of the factors affecting the capacity of B.C.G. to produce hypersensitivity. All tuberculin testing was done with purified protein derivative (P.P.D.), which has obvious advantages over Old Tuberculin. (Green[3] has pointed out that P.P.D. is less difficult to standardise and easier and less expensive to make.) The doses of P.P.D. were recorded in terms of tuberculin units (T.U.)—a simple system that avoids the cumbersome method of tenfold dilutions and numerous ciphers, one T.U. being equivalent to 0·00002 mg. of reference standard P.P.D.

It is usually thought that B.C.G. vaccine has to be kept cold and used very soon after preparation, that the potency of the vaccine can be adjusted by slightly changing the concentration of bacilli, and that large numbers of living organisms are needed to evoke satisfactory hypersensitivity. These beliefs, it now seems, are ill founded. Edwards and Gelting,[4] working for W.H.O. in collaboration with the Joint Enterprise and the State Serum Institute, Copenhagen, have shown that the capacity of the vaccine to cause hypersensitivity is little altered by storage for two months at 2°–4°C. After storage at 20°C for the same period the vaccine still produced what would normally be regarded as satisfactory tuberculin hypersensitivity; and even storage for a few days at 37°C had very little effect. It was suggested that the hypersensitivity from the stored vaccine might be temporary, but a year after vaccination there was no substantial evidence of this. B.C.G. vaccine can therefore be stored at moderate temperatures for quite long periods without much loss of potency. Edwards and Gelting[5] have also shown that, while sensitivity is not so great after vaccination with diluted vaccine, small changes in the concentration have hardly any effect, and even halving the concentration may reduce by only 1 mm. the mean diameter of the skin reactions. Moreover, the effect of dilution differs with different batches of vaccine, and one vaccine cannot always be made comparable with another by adjusting the amount of B.C.G. in each dose. Palmer describes as perhaps the most interesting and important investigations those on mixtures of living and dead bacilli. Vaccine containing 1 part of living and 255 parts of heat-killed vaccine produced strong hypersensitivity 10 weeks after vaccination, which persisted after a year. Heat-killed vaccine alone gave rise to only a low level of sensitivity; but even this was comparable with that recorded with presumed living vaccine in one country during the mass campaign. Thus large numbers of living bacilli are not necessary for "satisfactory" hypersensitivity. This may be the most important finding; but the most surprising is that the allergy-producing potency of B.C.G. vaccine was halved by exposure to sunlight in Denmark for only one hour.[6] Such deterioration may account for many of the unexpected results of vaccination projects throughout the world. The W.H.O. workers, therefore, have shown that the allergy-producing potency of B.C.G. vaccine is little reduced by the factors that were thought to be damaging, and greatly reduced by one that has only occasionally been mentioned.

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[1] Meyer, S. N., Hougen, A., Edwards, P. *Publ. Hlth Rep., Wash.* 1951, 66, 561.

[2] Medical Research Council, *Lancet*, April 19, 1952, p. 775.

[3] Green, H. H. *Ibid.* 1951, ii, 500.

[4] Edwards, L. B., Gelting, A. S. *Bull. World Hlth Org.* 1950, 3, 1.

[5] Edwards, L. B., Gelting, A. S. *Ibid*, p. 279.

[6] Edwards, L. B., Tolderlund, K. *Ibid*, 1952, 5, 245.

One might be tempted to conclude that B.C.G. is too variable and unstable for use in large immunisation campaigns; but the data so far collected relate only to the ability of the vaccine to produce tuberculin hypersensitivity. The relation of immunity to hypersensitivity is unknown, and the extent of immunity cannot be inferred from the skin hypersensitivity. Moreover, as Palmer says: "In many places in the world today vaccination is almost all that can be done to control tuberculosis, and B.C.G. is certainly the best known, the most promising, and the most acceptable immunising agent at our disposal." The controversy about the efficacy of this vaccine in the control of tuberculosis will be ended only by accumulating facts. Dr. Palmer's report shows how efficiently such facts are being gathered by international research.

Standards for Basal Metabolism

At the beginning of this century the German physiologist Rubner propounded the natural law that the heat generated by the metabolism of the resting individual is proportional to the surface-area of the body. This has proved a useful conception, which brings the metabolic rate of such different animals as the mouse and the horse approximately within the same range. It has also been used for predicting the normal basal metabolic rate (B.M.R.) in clinical examinations. But in the past few years it has become evident that, though the surface-area predicts the B.M.R. well enough, other measurements, which are easier to make and involve no elaborate formulæ, predict as accurately or even more so. For example, a good approximation is said to be given by a simple power of the weight—a power between 0·7 and 0·8 being ordinarily used in the calculation.[1–4]

Accurate knowledge of the normal B.M.R., and its variation with sex, age, race, stature, and environment, is valuable for two practical reasons. Firstly, the post-war food shortages in many lands and the increasing world population have stimulated studies of human energy requirements and of the basic physiological concepts behind such estimates. In persons not employed in heavy manual work, the basal metabolism may contribute up to half the total energy requirements. Clearly, it is essential to have accurate figures for the B.M.R. before estimating the food needed by various population groups. Secondly, the clinician who is called upon to treat a patient with an abnormal B.M.R. wants to know the normal value for a similar person under the same living conditions. In assessing disorders of the thyroid gland it is particularly important to know the limits of the patient's own normal range.

At the suggestion of Dr. W. R. Aykroyd, director of the Division of Nutrition of the Food and Agriculture Organisation, Dr. I. Leitch and a team from the Commonwealth Bureau of Animal Nutrition and Aberdeen University have reassessed the normal B.M.R. in relation to sex, stature, age, climate, and race.[5] They first collected details of just over 8600 B.M.R. measurements, of which roughly half had been made in people between the ages of 17 and 39. By means of multiple regression coefficients, they correlated B.M.R. with height, weight, surface-area, temperature, and humidity; and they have drawn up prediction tables for practical use. The B.M.R. of women was found to be almost exactly seven-eighths that of men of the same height and weight: between boys and girls the difference was slightly less. The effect of size was more complicated than either that of surface-area or of any simple function of height or weight. In this respect two main racial groups were defined—a group belonging to North America and Northern Europe, and a group belonging to India, China, and Japan. The two groups gave very different regression equations, and accordingly four prediction tables were drawn up—one for men and one for women in each group. Italians showed the same pattern as the American-European group, but with a higher average rate of metabolism. The Eskimo, the American Indian, and the Polynesian fell most easily into the Asiatic group, but their mean B.M.R. was higher than that of most of its members. Data for Australian aborigines were very variable. The authors seem to have found no systematic study of either African or American Negroes.

The prediction tables were prepared for a mean annual temperature of 70°F and a relative humidity of 75%. Starting from these points, the B.M.R. varied inversely with the temperature at the rate of 4 calories per °F in men and boys, and 3·5 calories in women and girls. It varied directly with humidity; in males by 3 calories for a 1% rise in humidity, and by slightly less in females. Maximum effects were observed when the climate was hot and dry or cold and wet. When all other variables had been taken into account, adults of both sexes and all race groups, and American-European children, conformed to the rule that the B.M.R. declines at the rate of 3% every ten years from the age of 3 to ages over 80. This is a higher rate of decline than has been reported in the past. There was no evidence of a significant change at puberty. When the observed rates, both in groups and in individuals in different parts of the world, were compared with predictions from the new tables and with previous estimates based on surface-area and body-weight, the tables showed the greater accuracy. Moreover, the tables and the correction factors for climate and age are easy to understand and simple to use.

In this issue we publish new standards set out by Dr. J. D. Robertson and Dr. D. D. Reid from a statistical analysis of the observed B.M.R. of 987 males and 1323 females. All these estimations were carried out personally by Robertson in London over the last twenty years, using a rigidly standardised technique. They prefer to express their results in terms of body-surface, and for practical use they give a table showing the expected mean, and upper and lower limits of normal, for each age and for both sexes. Curves representing the relation between B.M.R. per unit of surface-area and age show how closely the observed figures agree with the calculated expected mean. There are some interesting differences between the standards based on the observations of one man in London and those based on data from different sources

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1. Brody, S. Bioenergetics and Growth. New York, 1945.
2. Kleiber, M. *Physiol. Rev.* 1947, 27, 511.
3. Galvao, P. E. *J. appl. Physiol.* 1948, 1, 385, 389.
4. Collumbine, H. *Ibid.* 1949, 2, 640.
5. Quenouille, M. H., Boyne, A. W., Fisher, W. B., Leitch, I. Commonwealth Bureau of Animal Nutrition. Technical communication no. 17. 1951. 6s.

all over the world. Among Londoners the decline with age is apparently much greater in the earlier years and a little less in the later years than the uniform rate of 3% per decade. Thus a 10-year-old London boy has a B.M.R. 28% higher than that of a 30-year-old man. Similarly the B.M.R. of a London woman of any age is higher than the international average; it is about nine-tenths of the B.M.R. for a man. Are these significant physiological differences or the consequences of experimental error? Predictions of the B.M.R. for a few normal men and women of varying ages and sizes indicate that the London standards are usually 3–7% lower than the compound international standard. Is this a true local distinction? We may never get precise answers to these questions; though, if the issue is simply one of accuracy, our judgment would be in favour of the highly standardised technique of one skilled investigator.

It is certain that in future clinical pathologists in this country will use ROBERTSON and REID's standards, and that international food planners will use those of the Commonwealth Bureau; and each will have a closer approximation to the true answer than the previously accepted figures. The discrepancies between the two are unlikely to prove of great practical significance; and they can only be resolved by further observation and statistical analysis. Meanwhile we congratulate those who have worked with such thoroughness to establish both standards on the careful way in which they have sharpened the precision of fundamental physiological knowledge.

Ideas of Mind

"WHAT is mind? No matter," the old joke runs. "What is matter? Never mind." These, like many other age-old assumptions, have lately begun to crumble in the foundations. For what do we know of mind but that we experience part of its activities consciously, and that it is associated in some way with events in the brain? And how can we be sure that matter, which has dislimned into energy, is not an aspect of mind? Sir RUSSELL BRAIN assured those who heard his Rede lecture[1] that we are still far from being able to settle these questions.

In the last fifty years, he pointed out, medicine—particularly in its branches of neurology and psychiatry—has been actively changing our idea of the mind. Everyone knows that the brain influences the mind: the effects of drink, drugs, or a blow on the head demonstrate as much. Studies of diseases of the brain have contributed greatly to our knowledge of brain-mind relationship, and one striking discovery has been that the mind does not behave like something homogeneous. Damage to any part of the brain might be expected to make the mind in general less efficient; but, as we know from the results of destructive lesions, damage sometimes leaves the intellect untouched while changing the emotional life of the subject in such a way that his feelings for, and behaviour to, others are grossly abnormal. Again, the electro-encephalograph has revealed normal and abnormal electrical rhythms in the brain; and abnormal rhythms are sometimes found in people who have lapses—usually regarded as moral lapses—in the way of outbursts of temper or violence, or irresponsible behaviour.

This has important implications for our ideas of criminal responsibility. The law is based on the belief that the will is free: that man has the power to distinguish and choose between good and evil; so that if he does an evil thing he must have chosen to do it and can be held responsible. These principles are expressed in the McNaughten rules, which lay down that a person is to be held responsible for his act unless at the time when he did it, by reason of disease of mind, he either did not know the nature and quality of his act, or did not know that it was wrong. Neurophysiologists, however, can show that sometimes evil behaviour—such as a tendency to violent outbursts—is associated with recordable evidence of abnormal brain function; and modern psychiatrists find that a man who can distinguish good from evil may not always be free to choose between them. But it is one thing for doctors to recognise that a man's power to abstain from an evil act may be seriously impaired; it is quite another to bring this concept into a court of law. For there are—or so most of us think—sinners as well as sick men; and it is not easy for either lawyers or doctors to draw the line between pathological lack of self-control which does not deserve punishment and sinful lack of self-control which does. Perhaps, BRAIN suggested, the difficulty arises because of the retributive nature of punishment, which makes it necessary to assess responsibility: it would often be easier, he thinks, to decide whether a criminal was so mentally abnormal that he needed to be shut up for the protection of society, than to decide whether he was, through mental disease, so lacking in self-control that he deserved to escape punishment.

Apart from abnormal behaviour due to abnormal states of the brain, can the mind itself fall sick, or develop a pattern of thinking so far out of the true that it influences behaviour? In many forms of psychosis no gross brain abnormalities are found to account for the sick thoughts of the patient; but this may be merely because the lesion is too fine to be detected by our present methods, or because it is primarily a lesion in other organs than the brain—perhaps in the endocrine system. Nevertheless, while neurophysiologists and neuropsychiatrists have been concentrating on the physical basis of mind, a school of psychological thought has grown up which seeks to explain many forms of mental abnormality in psychological terms, and here again the study of the abnormal has thrown much light on the normal. BRAIN illustrated this development from Freudian psychology, because FREUD's "fundamental principles have been accepted far beyond the limits of his own school, and now form part of the equipment of most eclectic medical psychologists." FREUD introduced the idea that the mind can be analysed, and that it then appears to be composed of parts which behave as though they were autonomous, or semi-autonomous. He maintained that experience fraught with strong emotion might continue to influence behaviour, even when forgotten; and that feelings—such as anxiety—might persist, detached from the ideas which gave birth to them, or even attaching themselves to objects or circumstances with which they had originally nothing to do. Human behaviour, he believed, is sometimes, at least, the resultant of forces which, *though perhaps not actually measurable*, can be considered in quantitative terms. "We feel *justified in regarding emotion*," FREUD said, "as a quantity which may become increased, derived, or displaced." These emotional forces might be in conflict, and they might sometimes act on the subject in such a way as to determine his behaviour, even though he knew nothing about them consciously. This concept, too, strikes a blow at human responsibility, or at least poses some new ethical problems: what, for instance, is the moral position of a young woman who develops a hysterical paralysis which disables her from looking after an invalid mother?

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[1] The Contribution of Medicine to our Idea of the Mind. Delivered at Cambridge on May 7, 1952. London: Cambridge University Press. 1952. Pp. [illegible] 2s. 6d.

Thus we have been watching in this century, BRAIN said, the growth of two independent and very different explanations of mental states, which have in common only the disquieting suggestion that we are not such responsible parties as we thought we were. On the one hand the neurophysiologists and neuropsychiatrists are tending more and more to regard states of mind as caused by states of the brain; on the other hand, the analysts explain states of mind as the outcome of the interplay of psychological forces. Either they cannot both be right, or else there must be some logical expression of their relationship with one another. This brings us back to that same door wherein we went; for either we *must believe that brain and mind are two things* somehow related to one another, or they are two aspects of the same thing: we must, in short, be *dualists or monists*. SHERRINGTON, who was a dualist, believed that mind could never be explained in terms of matter, because the two are incommensurable. BRAIN thinks that we might perhaps get round the difficulty by altering the way we word our questions about it. Perhaps it makes sense to say that a certain state of the brain is not the *cause* of a pain or an idea but actually *is* a pain or an idea; and the feeling of pain, or the comprehension of the idea, is an experience of the person whose consciousness is related to that particular brain. The electrical pattern which we are trying to identify with these experiences is only a symbol for describing the behaviour of the brain as it might be observed by some other person with the necessary instrument. After all, as Sir RUSSELL has explained on a previous occasion,[2] the receptive function of the brain is to provide us with a symbolic representation of the physical world outside. If the only symbolic representation we can get of another person's idea is the electro-encephalogram produced by an electrical pattern in his brain—well, there it is: that is how someone else's idea looks to us. Fortunately we can always ask him how it looks to him; and since he *experiences it directly he is in a much* better position to describe it.

Ingenious as this monistic way of resolving the difficulty seems, it is apt to trickle through the head like water through a sieve leaving not so much as an electrical pattern behind. BRAIN himself seemed rather dissatisfied with it, for he hastened to point out another objection to monism. Before a feeling enters consciousness, nerve-impulses travel along relays of fibres, and during this process there is no feeling at all; and if the pathway is blocked at any point there never is any feeling. "So consciousness is not a property of all nerve fibres, even when they contribute to it: why, then, should it be related to some fibres and not to others? If mind and brain are two aspects of the same thing we might have expected that all brain-events would also in some way be mind-events, but this is not so, and we do not know why." Perhaps, he added hopefully, "brain-mind relationship will have to be expressed in terms of a space and time different from those of our naïve experience." *The space in which our mind exists may not be identical with the space in which we perceive the nervous system.* Perhaps its time is different too, for it seems that a sensation must have a certain duration if it is to be perceived at all: it is experienced only when a three-dimensional event persists for a minimum time. If so, a three-dimensional account of events in the brain would necessarily seem incommensurable with mind. Yielding cautiously to a more popular view of the problem, the lecturer described mind as the great amphibian, linked through the brain to the world of matter, but moving in its own sphere as though it could soar above the physical. Yet (he reminded his hearers) how vulnerable is this flying-fish: for a mindless agent—a germ, a drug, a weapon—can destroy it. Even the will, the very stronghold of mind, can be violated, as we have lived to see, so that a man will accept ideas he would normally reject, and confess to offences he has not committed.

We have much to learn; but meanwhile BRAIN warns us not to pursue either the physical or the psychological causation of mental states to the exclusion of the other. "Until the logic of their mutual relationship is established, the physical and *psychological treatment of mental disorders should be judged by their results, rather than by the theoretical expectations of their exponents.*"

Synergy of Health and Education

THE future historian, *looking back on our* Welfare State, may wonder why we were willing to spend almost as much money *on treating sickness as on educating* our children. He may even conclude that we had not yet recognised *the interdependence of health and* education—how the well-being of the child assists the teacher's task and a wise *upbringing forms the* firmest foundation for a healthy life. In theory our aims seem sound enough—JUVENAL summarised them 1800 years ago as *mens sana in corpore sano*—but practical application lags sadly behind. Our growing control over epidemic diseases and the rapid reduction in severe poverty should have *allowed us to embark* on a more constructive policy for health; and schools are among the most important means at our disposal for promoting fitness of mind and body. The school, indeed, should be a place where children "gain physical power as well as academic knowledge."[1] Yet all too many of our school buildings still stand as grim memorials of the grudging attack on illiteracy of fifty years ago. It is difficult to teach anything, and impossible to teach healthy ways of living, in these cramped and overcrowded classrooms. Even more important to the school than its buildings is the quality of its teachers; yet school teachers are ill paid, and too seldom have a chance to develop their teaching into a creative art capable of developing people who, in Dr. BROCK CHISHOLM's words, could "live at peace in an organised world."

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[2] *Lancet*, 1951, ii, 1073.

[1] Health of the School Child. Report of the Chief Medical Officer of the Ministry of Education for 1948 and 1949; p. 16.

At the Royal Sanitary Institute congress in Margate last month, Prof. A. V. NEALE advocated the teaching of health in and through the schools, as a combined operation by school doctors, practitioners, parents, and teachers, with school nurses and health visitors acting as vital links between each. The health instruction of parents is probably best given unobtrusively, in conversations with the school nurses, or during the school doctor's periodical inspections—if the pressure of routine tasks does not exclude all else. But if this instruction is informal it must be no less thorough, for well-meaning but ill-informed parental influence can do serious harm, through thoughtless threats that instil baseless fears ("Don't do that or Doctor'll take you away . . ."), insufficient sleep, or an ill-balanced diet, or through passing on errors that may affect the child's actions later in life regarding immunisation, "sex," childbirth, and so on.

In the fifty-odd years since the School Health Service began, the death-rates of children aged 10–15 have fallen from 2·1 to 0·56 per 1000, and the number of children under 15 dying of diphtheria has been reduced from 571 to 7 per million. The service cannot claim credit for all such reductions, any more than for the greater falls in neonatal deaths. But it has played a part in the improvement of maternal care, in the attack on diphtheria, and in limiting the spread of infectious diseases, including tuberculosis; and a big part in inculcating habits of cleanliness and building up the physique of our children. Replies to the "Twenty Questions" published in 1950 in the *Medical Officer* emphasised that no other system of civilian medical supervision covers the fit and the unfit so completely, or affords such opportunities for helping both the healthy children and the "lame ducks." As Dr. PETER HENDERSON, principal medical officer of the Ministry of Education, reminded the Margate congress, a public service cannot escape criticisms, and the school service has come in for its share. The main ones on NEALE's list are: over-concern with *routine* medical inspection; insufficient scope for inquiring and active minds; and the compiling of statistics which have little practical value. Such criticisms have led to suggestions for drastic reform: for example it is proposed that the service's clinical work should be transferred to practitioners and pædiatricians under the supervision of the physician for child health at the area teaching hospital (that is, making the school service of each area an extension of the appropriate hospital's child-health department); or that most of the school doctors' work should be handed over to nurses, or the nurses' work to social workers, releasing the nurses for hospital work.

Because of the strategic importance of the school as a place for promoting healthier living, it would seem natural for the School Health Service to be one of the most active and creative parts of medicine. But at a time when every item of our health budget is closely scrutinised it must clearly show that it is not merely duplicating and overlapping the work of general practitioners in the N.H.S.; otherwise neither sentiment nor records of past work well done can save it. In its earlier years, as the "School Medical Service," it kept an eye on the children with parents too poor to pay a doctor, seeking their undetected ailments and developing expedients for treating them; but here the N.H.S. has changed the picture, for no child now lacks medical attention, at home or in hospital, simply because of poverty. The change of name to "School Health Service" in 1944 marked a new concept of the service's work as ancillary to the educationist's in promoting health of mind and body. But the further reorganisation needed to meet the changed situation since 1948 is less obvious. Some of the service's original clinical purpose has disappeared or been transferred; yet its methods of working seem much the same. Can it show that the benefit derived from routine medical inspections justifies the expenditure in doctors' time? It is true that only 241 doctors give their whole time to the school service, while 1246 doctors in the local health services work part-time in it, as do 501 general practitioners—a total medical staff of 1988, equivalent to 907 full-time medical officers. In 1950 these doctors examined 2 million school-children and re-examined $2^1/_2$ million; yet even so, Dr. HENDERSON pointed out, the periodic examinations occupy less than half the time of most school doctors. Most of these, in HENDERSON's experience, are keen, competent, and hard-working, besides having a good hospital and public-health training; and great advantage can result from inspections bringing together parent and teacher, nurse and doctor, in the interests of the child. Where an experienced and interested doctor really sets out to make partners of the nurses and teachers in this enterprise these advantages are realised; but admittedly the rituals of medical inspection can be preserved without this being achieved. Inspection can take place without adequate information about school performance or frequency of absence from school. Recent studies have revived interest in school absence as a useful index of need for social and medical care. There is need for experimentation with methods of canalising the teacher's daily experience of the child's performance, so that it may routinely be brought to the notice of medical and nursing colleagues.

The school doctor often moves on to other administrative duties just when he has gained the experience needed to do a good job. So far the opportunities have attracted few doctors willing to make a life career of school work. Not only the terms of service but the work itself, in its monotonous routine mould, is unattractive except to a few enthusiasts. Some more direct approach to the whole individual, of which SHELDON's somatotyping is a pioneer venture in young adults, might be a partial answer. A more thorough training in behaviour disorders in their early stages would increase interest, and there would be plenty of material despite the dwindling in number and severity of physical defects. The need is for a sustained and self-critical attempt by the Ministry and local education authorities to review the methods and objectives of the service in the light of current requirements.

Annotations

"CAT-SCRATCH FEVER"

SINCE we last referred to French and American observations on "cat-scratch fever,"[1] our challenge to report cases diagnosed in this country has been answered[2]; and in this issue Dr. Campbell and Dr. Wheaton give an account of the disease as it affected one of them. The name of this syndrome should be settled before the present misleading term is too widely adopted. Of 42 cases described by Mollaret and his colleagues[3] only 21 resulted from scratches or bites by cats, while in a further 5 these animals were kept in the household but there was no history of injury. In some of the remaining cases the illness followed injury from bone, wood, or metal splinters or various sorts of thorn, or a mosquito bite. These workers have suggested the title "benign lymphoreticulosis of inoculation." This is certainly less misleading but is open to the objection that in some cases there has been no evidence of inoculation, while in others infection has almost certainly taken place via the upper respiratory tract.[3 4] Possibly "benign lymphoreticulosis" is a more suitable—though still inexact—label.

The main, and apparently constant, feature of this disease is distinct swelling of a lymph-gland or group of glands. Suppuration may be apparent only histologically, but commonly fluctuation is obvious and pus may be discharged through one or more sinuses. The differential diagnosis will be influenced by the site involved; and Daniels and MacMurray[4] say that in their cases the initial clinical impression was of tuberculous or pyogenic adenitis, glandular fever, or lymphadenoma or other tumours. Some of the earliest American cases were first diagnosed as ulceroglandular tularæmia.[5] It should be remembered that infection with *Spirillum minus*[6] and with *Pasteurella septica* can be transmitted to man by bites from cats. The epitrochlear and axillary glands or those of the head and neck are most commonly involved; but when the condition presents as an enlarged mass in the inguinal region confusion with venereal disease—particularly lymphogranuloma venereum—is likely. In such circumstances there may be no superficial lesion indicating the type of infection; in lymphogranuloma the small genital ulcers will usually have disappeared, and in the non-venereal condition a history or evidence of injury to the skin may be lacking. [illegible] pitfall is strikingly exemplified in a case [illegible] et al.[7] A young woman who was returning to France by sea from a distant country first noticed a swelling in the groin while she was staying for a few weeks in a port on the route. This swelling increased, and during the second part of the journey she consulted the ship's doctor who immediately placed her in strict isolation and, after some delay, reluctantly gave his diagnosis as bubonic plague which was atypical because of the sulphonamides with which the patient had been treating herself. Some days later this diagnosis was replaced by lymphogranuloma; and the same diagnosis was made in the case of another passenger, an engineer of 42, with a large suppurating inguinal mass. Efforts by the doctor to gloss over the epidemiology of this disease by reference to "*la douceur des nuits de l'Océan Indien*" only aggravated an already stormy situation, and divorce was seriously considered by the engineer's wife. On arrival in France both patients were found to have played with the cats, of which there were a number in the first ship, and both gave positive skin reactions to the "cat-scratch" antigen and, by contrast, negative Frei tests. One may wonder how often this disease has been mistaken for lymphogranuloma.

The causative organism has not been discovered, and attempts to culture bacteria or fungi from pus and lymph-glands have all been fruitless.[4] Mollaret and his associates[3] continue to find evidence in support of their opinion (shared by some American workers) that a virus of the psittacosis-lymphogranuloma group is the causal agent. Certainly lymphogranuloma and the "new" disease have features in common—a primary site of inoculation, regional adenopathy with suppuration, and intradermal reaction to autogenous pus—but proof of a similar causation will depend on isolating from the lesions of cat-scratch fever a Castaneda-positive virus with the heat-stable group antigen which characterises the many different viruses in this group. Experimentally the French workers have demonstrated in such lesions intracellular particles which in size and shape resemble those of the psittacosis-lymphogranuloma virus group. Such findings must, however, be interpreted cautiously in view of the difficulty of distinguishing the fine basophilic granules of tissue mast-cells. Moreover, in these studies the negative results with Macchiavello's stain and the occasional abundance of particles contrasts with the findings in lymphogranuloma.

A positive reaction to intradermal inoculation of heat-inactivated pus from cases of cat-scratch fever has been observed regularly in both French and American series.[3 4] In lymphogranuloma inoculation of suspensions of a heterologous virus usually elicits skin reactions comparable with those produced by the infecting agent[8]; the group antigen dominates. By contrast, none of the patients with cat-scratch fever have shown positive Frei tests, whereas four patients known to have lymphogranuloma failed to react to cat-scratch antigen. Although it is possible, as Willcox[9] suggests, that reactions to this antigen may occur in other conditions, the complete absence of dermal cross-reactivity between cat-scratch fever and lymphogranuloma is strong evidence against the former being caused by a related virus. A group-reactive antigen made from the [illegible] lymphogranuloma venereum has been used for [illegible] on sera in cases of cat-scratch fever.[3 4] Mollaret reported positive results in 20 out of 43, the serum titres ranging from 1 in 10 to 1 in 160. Most of these patients were tested once only, but in one a twofold increase in strength was found; and in two, titres of 1 in 10 or 1 in 80 were detected after a previous negative test. In view of the fact that in psittacosis-lymphogranuloma infections the group antibody, like the Frei reaction, often persists for a long time, so that positive findings may be unrelated to the disease, it would be rash to ascribe any definite significance to the presence of antibody in less than half the cases, and (except for one instance) in low or moderate strength. Furthermore of the 12 cases studied by Daniels and MacMurray, only 3 had a positive complement-fixation test, and fixation was not complete at dilutions above 1 in 16 or 1 in 32. Of these none showed a rising titre, while the negative results were from sera collected 14–180 days after the appearance of enlarged lymph-glands.

Thus the evidence that the agent causing cat-scratch fever belongs to the psittacosis-lymphogranuloma group is incomplete.

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1. *Lancet*, Feb. 9, 1952, p. 302.
2. Cox, P. J. N. *Ibid*, Feb. 16, 1952, p. 361. Wigley, R. D. *Ibid*, p. 365. Garai, O. F. *Ibid*, March, 29, 1952, p. 646.
3. Mollaret, P., Reilly, J., Bastin, R., Tournier, P. *Pr. méd.* 1951, 59, 681; *Ibid*, p. 701.
4. Daniels, W. B., MacMurray, F. G. *Arch. intern. Med.* 1951, 88, 736.
5. Foshay, L. *Lancet*, March 29, 1952, p. 673.
6. Beaumont, G. E. *Ibid*, April 5, 1952, p. 718.
7. Siguier, F., Welti, J.-J., Lumbroso, P. *Bull. Soc. méd. Hôp. Paris*, 1952, 68, 216.
8. Bedson, S. P., Barwell, C. F., King, E. J., Bishop, L. W. J. *J. clin. Path.* 1949, 2, 241.
9. Willcox, R. R. *Lancet*, March 1, 1952, p. 470; *Ibid*, March 29, 1952, p. 673.

CENTRAL HEALTH SERVICES COUNCIL

Annual reports, like bottled beer, should not be kept over-long from the consumer. The account of the work of the Central Health Services Council in 1951[1] seems a little flat because the council has largely restricted itself to matters referred to it by the Minister of Health, and in some cases administrative action has long ago been taken on the strength of its findings. Moreover one of its most useful inquiries, on integration of the various services,[2] was published separately a few weeks ago.

Early in 1951 the council's Standing Dental Advisory Committee found no evidence of a decline in the demands on the general dental services. It decided, too, that there was no immediate hope of substantially increasing the number of dentists beyond the existing total. "The immediate object," the committee concluded, "should be to correct the present imbalance and to secure that the limited services available were used where the need was greatest." If dentists were to devote more time to the priority classes, the demand by the non-priority groups must be curtailed, without, however, deterring people from seeking conservative treatment. "This meant, in effect, reducing the demand for dentures." The committee formed the opinion that, in any case, too great a proportion of dentists' time was being devoted to denture work, and it suspected that some of the demand was unreasonable. On the credit side the committee found, from observation of the experimental scheme for training and employing oral hygienists, that these ancillaries "could be satisfactorily trained and usefully employed in the public dental service"; and it suggests that their contribution "more than justifies the small diversion of teaching resources which the training requires."

COUGH MIXTURES

Cough remedies are still one of the most popular forms of medication, even though the value of many of them is open to doubt. Dunlop et al.[3] have found that of 17,301 prescriptions under the National Health Service, 1382 were for cough mixtures. The lungs seem to rank second only to the stomach in the need for medicinal aid, and cough mixtures are probably used as placebos more often than any other medicines except tonics. There can, for example, be few patients with a common cold who, if they seek medical advice, are not allotted a bottle of cough-cure. Then there is the elderly bronchitic who regularly demands his favourite nostrum and is not easily denied it. The public like their cough medicine; and if refused by the doctor they will go round the corner to the chemist.

In Dunlop's analysis purely expectorant mixtures were prescribed more than twice as often as purely sedative remedies; but of the 1382 prescriptions, 806 were for remedies containing both sedative and expectorant drugs. This, says Dunlop, indicates some therapeutic confusion; but it might also reflect an attitude of therapeutic nihilism. Such an attitude is unfair to the sedative group of drugs, such as codeine and amidone. On the other hand, it was shown some time ago[4] that the commonly used expectorants, such as potassium iodide, ammonium salts, ipecacuanha, and senega, are virtually useless. Evidence to the contrary has been based either on uncontrolled clinical impressions or on animal experiments in which the drugs were given in very large doses which, if translated into clinical practice, would be emetic. A real expectorant is badly needed; and in this respect the work of Armstrong and White[5] with deoxyribonuclease is encouraging, for this enzyme strikes at the root of the matter by liquefying deoxyribonucleoprotein—the component which chiefly accounts for the viscosity of purulent sputum. Deoxyribonuclease can be obtained from ox pancreas, rice bran, or yeast. It is administered by spray inhalation, and the results in the first clinical tests were encouraging. Streptodornase, one of the enzymes present in concentrates from cultures of hæmolytic streptococci, has a similar action on deoxyribonucleoprotein. Such liquefaction of purulent bronchial secretions promises to be a good deal more effective in enabling a patient to clear his air-passages than adding mucus to them, which is what the present expectorant drugs are supposed to do. Banyai[6] asserts that inhaled carbon dioxide, in a 5% mixture with oxygen, is an effective expectorant, which not only stimulates respiration and increases bronchial peristalsis but "liquefies mucopurulent inflammatory exudates." Banyai's work seems to have attracted little attention, though he first described it eighteen years ago.[7]

DIABETES AND STRESS

Good diabetic control is usually described in terms of accurate adjustment of insulin dosage to a regular prescribed diet. This, of course, is the basic factor; but even with a carefully devised régime the severity of the diabetes may fluctuate widely, so that the condition remains grossly unbalanced. Such changing insulin requirements are commonly associated by the patients themselves with domestic upheaval, strained circumstances at work, or other worry; and this aspect has been studied at several large diabetic clinics, and notably at the New York Hospital.

To obtain a basis for comparison Hinkle and Wolf[8] first investigated non-diabetics and found that in the fasting normal person at rest there was initially little change in the blood sugar and ketone concentrations or rate of urine output; but later in the fast day the blood-sugar fell slowly to 40–50 mg. per 100 ml. and the blood-ketone concentration rose. At about the same time there was moderate diuresis. Similar changes took place in normal people in stressful situations without starvation. Hinkle and Wolf carefully avoid implying that the emotions occasioned by the stress caused these metabolic changes; but they did notice a correlation between anxiety and diuresis, and between anger, dejection, resentment, or loneliness and a rise in blood-ketones. In diabetics the metabolic response to psychological stresses was similar but often greater. Moreover "stress diuresis" associated with anxiety may be induced in diabetics whether or not they have glycosuria.[9] On the other hand, under basal conditions, up to 7% glucose can be passed in the urine without polyuria.[8] The usual initial reaction of a fasting diabetic to a stress situation was a transient fall in blood-sugar, occasionally great enough to cause hypoglycæmic symptoms, and an increase in blood-ketones. If the stress persisted the blood-sugar was likely to rise,[10] especially when fear or anger were prominent features of the emotional response. Carbohydrate tolerance was also found to be affected by stress. Circumstances associated with resentment or sadness tended to accentuate the diabetic type of glucose-tolerance curve, whereas with less stress or with anxiety the sugar-tolerance was not so impaired. Diabetics with initially high blood-sugar levels reacted to conflicts by a rapid rise in blood-ketones and greatly increased secretion of water, glucose, ketones, chloride, and fixed base. In this way the metabolic changes typical of diabetic ketosis can develop rapidly[11]; and in fact episodes of diabetic ketosis are often connected with stressful situations.[12]

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[1] Report of Central Health Services Council for the Year Ended Dec. 31, 1951. H.M. Stationery Office, 1952. Pp. 28. 1s. 3*d.*

[2] Report on Coöperation between Hospital, Local Authority, and General Practitioner Services. H.M. Stationery Office, 1952. See *Lancet*, April 26, 1952, p. 860.

[3] Dunlop, D. M., Henderson, T. L., Inch, R. S. *Brit. med. J.* Feb. 9, 1952, p. 292.

[4] Alstead, S. *Lancet*, 1939, ii, 932; *Ibid.* 1941, i, 308. Boyd, E. M., Palmer, M. E. *Acta pharmacol. toxicol.* 1946, 2, 235.

[5] Armstrong, J. B., White, J. C. *Lancet*, 1950, ii, 739.

[6] Banyai, A. L. *J. Amer. med. Ass.* 1952, 148, 501.

[7] Banyai, A. L. *Amer. Rev. Tuberc.* 1934, 30, 642.

[8] Hinkle, L. E. jun., Wolf, S. *J. Amer. med. Ass.* 1952, 148, 513.

[9] Hinkle, L. E. jun., Edwards, C. J., Wolf, S. *J. clin. Invest.* 1951, 30, 818.

[10] Dunbar, F. Emotions and Bodily Changes. New York, 1946; p. 186.

Diabetes, when it first presents, commonly does so in a setting of stress, such as a reverse in business or loss of a near relative. At the time of the flying bombs such stress reactions were very evident in London diabetic clinics. A near miss from a flying bomb might score a direct hit on the diabetes, which would temporarily require greatly increased doses of insulin. Such factors should not be forgotten in the less dramatic conditions of peace; for helpful general advice and understanding can do much to lessen the fluctuations in the disease.

INTRAVENOUS ADMINISTRATION OF FAT

COMPLETE parenteral feeding is feasible; for not only carbohydrates, proteins, and vitamins, but also emulsified fats, can be administered intravenously. Thus an unconscious or badly injured patient can be kept alive for weeks or even months without recourse to oral feeding. Stare and his colleagues[13] at Harvard kept a badly shocked patient alive for 67 days by daily intravenous infusions of fluid containing fat emulsion, glucose, and protein hydrolysates; the fat provided 1200 calories daily and the other components 1100 calories.

There are two major problems in intravenous feeding: the prevention of thrombophlebitis, and the provision of enough calories in a limited quantity of fluid, since with too large a volume the patient will be waterlogged. Carbohydrate and protein in high concentration will cause withdrawal of fluid from the tissues and irritate the vein into which the infusion is made, possibly with ensuing chemical thrombophlebitis. This difficulty does not arise with fat emulsions. Emulsified fat particles do not exert an osmotic effect and may be injected in high concentrations in a relatively small volume of fluid. Thus it is possible to provide 1600 calories a day in fat emulsions alone.

Johnson et al.[14] have shown that unsuitable emulsifying agents, such as sorbitan monolaurate, may cause phlebitis or irritation of the tissues around the vein. A concentration of 10% seemed to be most suitable; higher concentrations produced a decreased platelet-count and a prolonged bleeding-time. The most common reaction to fat emulsions was pyrexia, which was noted in about a third of the patients. The temperature began to rise just after the injection, quickly reached a peak, and within four to eight hours returned to normal, thus following the course of a typical pyrogen reaction. Anorexia, nausea, vomiting, diarrhœa, and headache occurred in some patients with a pyrexial response. A few developed lumbosacral pain, urticarial reactions, and shortness of breath. Mild anæmia has also been reported after the continued infusion of fat emulsions. Johnson and his colleagues observed that emulsions did not give pyrogen reactions if injected immediately after preparation, but did so if they had been stored, even if they had remained sterile. The emulsifying agents were thought to be the most probable source of pyrogens. In no case was there evidence of renal damage or impairment of liver function.

In a later study Johnson and his colleagues[15] investigated the fate of emulsified fats administered parenterally to normal people and to patients with renal insufficiency, hyperthyroidism, or cirrhosis of the liver. In normal persons 75% of the fat was removed from the circulation by the end of the infusion—that is, after two hours—but the remainder was removed only after another eight hours. In patients with renal impairment fat disappeared more slowly from the blood-stream; while in thyrotoxic patients it disappeared more rapidly. The blood-fat was lower than normal in patients with cirrhosis of the liver. Dogs made diabetic with alloxan had a higher blood-fat than normal dogs or insulin-treated diabetic dogs—which is in keeping with the observation that lipæmia is common in uncontrolled diabetics.

The parenteral administration of fat is not new—it was described in Japan over thirty years ago—but difficulties of manufacture, storage, and transport of the emulsions have prevented its widespread practice. These latest studies show, however, that the injection of freshly prepared emulsions, using suitable emulsifying agents, is reasonably safe and should be considered whenever parenteral feeding has to be continued for some time.

THE OXFORD SYMPOSIUM

SOME years ago a sentimental fancy led us to liken the first symposium of the Society for General Microbiology to those international disputations of the 13th-century scholars who gathered on Mont St. Geneviève to hear Dr. Profundus and Dr. Perspicuus devoting their learning and logic to immensely interesting topics of no practical importance whatsoever. Since Oxford is thought to have its origin as an academical retreat in the migration of certain schoolmen who had made Paris too hot to hold them, it was pleasant that the society's third symposium should draw to the banks of Isis scholars from Brussels, Paris, Stockholm, Rome, Coimbra, Illinois, Chicago, Ontario, and even Cambridge. They came to discuss the nature of virus multiplication, and this is certainly a subject which justifies the methods of the symposium. From the time that Stanley showed the virus of tobacco mosaic to be a crystalline mass of nucleoprotein it was clear that the little which we knew (and know) about bacterial multiplication cannot be applied lock, stock, and barrel to viruses. Chance and ingenuity have provided new techniques in a field shared and not yet disputed by bacteriologist, biochemist, and geneticist, and the complexity of the problem has attracted sparkling minds from all the biological sciences.

Long ago in 1947 (such is the notation of these active minds) Luria brought forward evidence suggesting that the unit of multiplication of bacteriophage is much smaller than the infecting particle which attaches itself to the host bacterium. A year later Hoyle demonstrated a similar phenomenon in influenza virus inoculated upon the allantoic membrane. Others have dotted the *i*s, and the sum of their information indicates that the self-replicating unit is a fragment of nucleoprotein and no more. It is here that we reach the edge of the intellectual precipice. No-one knows "how" larger and organised bodies reproduce themselves; but it is done by rule and some part of the mechanism we can observe. Is the multiplication of virus essentially the same process on a smaller scale and shorn of all complications? Does it depend on the host as much as on the parasite? If A. E. Boycott had not pointed out long ago that at this level "live" and "dead" cease to carry their usual meaning, we might ask whether the replication of nucleoprotein is a chemical or a biological process. This symposium did not provide an answer, but it gave an opportunity for thoughtful men to ask the question and share surmises which they would put on paper with diffidence. It was incidentally a reminder that research is done not so much in glass and concrete palaces as in the human forebrain.

THE next session of the General Medical Council will open on Tuesday, May 27, at 2 P.M., when Prof. DAVID CAMPBELL, the president, will deliver an address. The Medical Disciplinary Committee will sit on Wednesday, May 28, at 2 P.M.

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[11] Hinkle, L. E. jun., Wolf, S. *Amer. J. med. Sci.* 1949, **217**, 130.
[12] Hinkle, L. E. jun., Evans, F. M., Wolf, S. *Psychosom. Med.* 1951, **13**, 160, 184.
[13] Van Itallie, T. B., Waddell, W. R., Geyer, R. D., Stare, F. J. *Arch. intern. Med.* 1952, **89**, 353.
[14] Johnson, W. A., Freeman, S., Meyer, K. A. *J. Lab. clin. Med.* 1952, **39**, 176.
[15] Johnson, W. A., Freeman, S., Meyer, K. A. *Ibid*, p. 114.

Special Articles

THE PREVENTION OF DENTAL CARIES BY THE ADMINISTRATION OF FLUORINE IN PUBLIC WATER-SUPPLIES *

E. F. W. MACKENZIE
O.B.E., M.C., M.B. Edin., D.P.H.
LIEUT.-COLONEL, R.A.M.C. RETD ; DIRECTOR OF WATER EXAMINATION, METROPOLITAN WATER BOARD

THE mechanics of dentistry have reached a high state of efficiency: and it may be that, when the National Health Service is able to provide early conservative treatment for all defective teeth, the effects of dental caries will become less serious. But this hope cannot justify an attitude of complacency towards the most prevalent disease in civilised communities.

The ideal method of preventing a disease is first to find and then to remove its cause. Unfortunately we have no precise knowledge of the fundamental causes of dental caries; which may be the result of any or all of a number of influences. Members of the same family, reared under similar conditions of diet, oral hygiene, and general environment are sometimes at opposite extremes in their powers of resistance to caries. The comparative freedom of some more primitive races (Mellanby and Mellanby 1952) suggests that this infliction may be a product of the habits associated with what we are pleased to consider our advanced state of civilisation. In this state of uncertainty we cannot afford to neglect any measure that might help to control this distressing and almost universal disease.

I believe that there is a simple and inexpensive way of reducing the incidence of dental caries—namely, by supplementing the daily intake of fluorine in areas where this is insufficient. I also think that, in the existing state of our knowledge, the way to ensure the greatest benefit to the greatest possible number would be to add fluorine to public water-supplies. But before any responsible authority could support such a step, satisfactory answers must be found to the following questions:

(1) How much benefit to the population may reasonably be expected?

(2) What concentration of fluorine in the public water-supply will give sufficient benefit to justify its administration?

(3) May this concentration reach the level at which the known harmful effects of fluorine become evident?

(4) With what degree of accuracy can the dose of fluorine in the water be regulated? Can the desired dose be maintained with the certainty that it will never exceed the limit of safety?

(5) Is the public-water supply the most suitable and most effective vehicle for fluorine?

(6) What will be the cost?

The answers to these questions are to be sought in the voluminous and often contradictory literature on the subject. Much of this published work is open to criticism because the period of exposure to fluorine has not been explicitly determined; because the fluorine content of the water, which may fluctuate appreciably, has been based on an insufficient number of examinations; because the methods sometimes used for estimating the fluorine content were subject to error; or because the severity of the lesions now known to be associated with fluorine has not been precisely recorded. The literature must, therefore, be critically examined and I shall refer to only a few publications, which I have chosen mainly because the findings are supported by acceptable evidence or because they have since been confirmed by other independent investigations.

The Evidence

MOTTLED ENAMEL

The dental dystrophy known as mottled enamel has probably existed from earliest times, but it did not receive much attention until the work of Black and McKay (1916) was published. Black described a dental lesion which he found in 80% of the permanent residents of Colorado Springs in the U.S.A., but not in those who had moved there during adult life. He described the affected teeth as follows:

> "The lingual surfaces . . . were generally an opaque paper white but mottled with normal spots and clouded areas. The labial surfaces were in part of an abnormally white color resembling white unglazed paper, but a considerable portion of the surface was mottled with dark brown. Some had black bands running across the labial surface."

In severe cases the teeth appeared absolutely black.

It is now recognised that the condition may exist in any degree from a slight loss of the smooth translucency of healthy enamel, recognisable only with a lens and a powerful light, to the state described by Black, to which, in extreme cases, severe pitting and deformity of the teeth through attrition may be added.

McKay (1918) thought that mottled enamel was connected with the drinking of water from artesian wells.

Ainsworth (1928, 1933) reported mottled enamel in the inhabitants of Maldon in Essex. The condition did not affect those who lived more than 3 miles from Maldon, or who were born outside the area and moved to Maldon after the age of eight. Dental caries was less common than elsewhere in both deciduous and permanent teeth of the Maldon children, although the deciduous teeth were not mottled. Ainsworth thought that something affected the teeth during their development and caused the mottling, and that this something might be in the local water-supply. Both these suppositions have proved correct.

The relation between mottled enamel and water-supplies was perhaps most conclusively established by Kempf and McKay (1930).

The town of Bauxite in the U.S.A. was established in 1901, and the water-supply originally came from shallow wells and springs, but in 1909 a deep well was sunk, and the supply was later augmented by two other deep wells, the water being piped to the houses. The shallow wells were gradually abandoned. The authors found no evidence that mottled enamel had existed before the introduction of the deep-well water, and the oldest person with this defect had been born about the time this water came into use. This investigation was particularly convincing because the food-supply of the town came from a central store or from locally grown produce, and the diet of the affected people remained unchanged throughout. Moreover, children of all social classes, and therefore of all conditions of diet, were attacked equally, regardless of their physical condition, but children who lived outside Bauxite and who did not drink water from the new wells were not affected. Analysis of the water threw no light on the cause of the condition and, after studying the chemical composition of the waters previously examined by Black and McKay (1916), the authors came to the conclusion that the mineral content of waters in areas where mottled enamel was common could vary widely. They suggested that animal experiments might "indicate definitely whether the water carries some deleterious agent or lacks something necessary for the normal growth of the enamel."

FLUORINE AND MOTTLED ENAMEL

At this point in the story it was reasonable to infer that mottled enamel and caries resistance were caused by

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* Abridged from a Chadwick public lecture delivered on March 4, and published by kind permission of the Chadwick Trustees. The opinions expressed are the author's, and not necessarily those of the Metropolitan Water Board.

the same agent in the water; but what this was had not been established nor was it even suspected that the beneficial effects might be obtained without dental disfigurement.

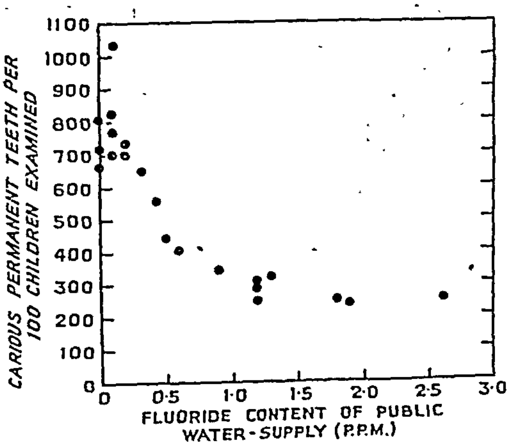
McCollum et al. (1925) found that the dentition of rats was improved by giving them a diet rich in fluorine, but that a dental dystrophy with yellow discoloration of the teeth also developed. It was not until six years later that three independent studies by Churchill, Smith et al., and Velu (quoted by Dean and Elvove 1935) demonstrated that fluorine was the cause of mottled enamel. The inference was justified that fluorine was also responsible for the increased resistance to dental caries which accompanied this condition. The more definitive name of dental fluorosis was then applied to the lesion. Following these discoveries Ainsworth (1934) reported that the water at Maldon contained 4·5 to 5·5 parts per million (p.p.m.) of fluorine.

It is interesting to recall that Crichton-Browne (1892) suggested that the increasing abstraction of bran in the milling of white flour was a cause of dental caries. He quoted Dr. George Wilson's observation that the husky parts of wheat were the main source of fluorine in the diet. He *regarded fluorine as an essential constituent of normal enamel,* and he thought that its addition to the diet might reduce the incidence of dental caries. He went so far as to say: "I think it well worthy of consideration whether the re-introduction into our diet . . . of a supply of fluorine in some suitable natural form might not do something to fortify the teeth of the next generation."

HIGH-FLUORINE WATERS, MOTTLED ENAMEL, AND CARIES RESISTANCE

Following the discoveries I have mentioned, extensive surveys were made in the U.S.A. to ascertain more precisely the relationship between mottled enamel, caries resistance, and fluorine in water—notably those of Trendley Dean and his co-workers (Dean 1933, 1938, Dean and Elvove 1935, 1937, Dean et al. 1934, 1935, 1939, 1941, 1942).

It is doubtful whether such a comprehensive investigation of the incidence, ætiology, and significance of any other condition has ever been made in so short a time. Largely as a result of these officially sponsored surveys it is now known that waters naturally containing the fluoride ion in concentrations of from 1 to 8 and even 10 p.p.m. have for long been in regular use for domestic and industrial purposes. It has been shown quite conclusively, particularly by Dean's series of over 7000 children, that the incidence of dental decay is inversely proportional to the fluorine content of the water-supply (fig. 1). Dean has shown, moreover, that a 50–65% reduction in the incidence of caries in school-children may be expected from concentrations of fluorine of between 1·0 and 1·5 p.p.m., a level that causes either no mottling of enamel or so slight a degree that it is noticeable only on expert examination. He also found that no further appreciable benefit was conferred by raising the fluorine content above this level. It is of interest to note that the maximum concentration he proposed is also the permissible limit of fluorine in potable water as laid down in "Drinking Water Standards 1946" (American Water Works Association 1946).



After TRENDLEY DEAN

Fig. 1—Relation between carious permanent teeth found in 7257 school-children aged 12–14 in 21 United States cities and the fluorine content of the public water-supply.

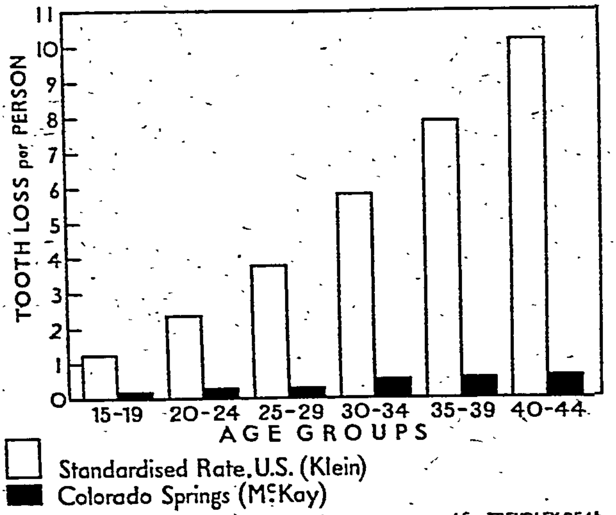
No surveys have been made in England on a comparable scale, nor would they be possible owing to the scarcity of natural water with a high fluorine content. Nevertheless, Weaver (1944) made an interesting comparison between the incidence of dental caries in the children of South and North Shields. He found that the water supplied to South Shields contained 1·2–1·8 p.p.m. of fluorine and in North Shields 0·25 p.p.m. (It should be mentioned that Forrest et al. (1951) found only 0·82 p.p.m. in South Shields and 0·07 p.p.m. in North Shields, these figures being the average of 46 and 26 samples respectively drawn at intervals over a period of months.) In most other respects these towns are believed to be similar. A group of 500 children was studied in each town, one aged five years and the other aged twelve years. The incidence of caries in both the deciduous and the permanent teeth of the children of South Shields was over 50% less than in those of North Shields, and Weaver (1948) said "my own findings in South Shields fit in very well with Dean's"; but later he considered the benefit to be less than before and attributed this to nutritional changes (Weaver 1950).

Weaver (1950) also examined some West Hartlepool children where the water contained 2·0 p.p.m. of fluorine; he found less caries than in South Shields, but there was a degree of mottled enamel which in some cases amounted to disfigurement. At South Shields he observed pigmentation of the enamel in only 2 out of 500 twelve-year-old children. Weaver's investigations at South Shields originated in an observation by a dentist that the children who were evacuated from that town during the war had remarkably good teeth.

Bromehead et al. (1943) reported that many of the cases of mottled enamel they saw during a large survey in England were in areas where the drinking-water contained no more than 0·3 p.p.m. of fluorine. Spira (1942) found the defect in 22% of 5019 Service men and women examined in England—a fairly representative sample of the population from 60 different counties in England, Scotland, and Wales—yet mottled enamel is hardly noticeable in this country except in a few endemic areas. Such findings are at variance with the bulk of the evidence.

There is some disagreement in these surveys about the concentration of fluoride ion required, on the one hand, to give maximum protection against caries and, on the other, to cause symptoms of dental fluorosis. These differences may be caused by such variables as the relative intakes of calcium and fluorine, the intake of vitamins, and the general nutritional state (McClure and Mitchell 1931, Shortt et al. 1937*a*). On the whole, however, the evidence does not suggest that such factors have played an important part in English and American communities, and the differences are more likely to be the result of the errors to which the investigations are open.

Dean et al. (1935) classified mottling in six grades according to the degree present, and there can be no doubt that unless some such classification is adopted differences will exist in the observed incidence. I shall consider only the possibility of disfigurement and whether it will be



After TRENDLEY DEAN

Fig. 2—Tooth loss in 400 adults at Colorado Springs (mean annual fluorine content of water 2·5 p.p.m.) compared with standardised rate.

sufficiently common or severe to offset the advantage of a substantial reduction in caries. It is safe to say on the evidence that this will not be the case if the water contains no more than 1·5 p.p.m. of fluorine. There is general agreement with Dean's finding that the maximum benefit without risk of disfigurement or other undesirable consequences may be expected at concentrations of between 1·0 and 1·5 p.p.m.

White flecks in the enamel occasionally appear with concentrations of 1·0 p.p.m., but Parfitt (1951) thought that there was no indication that these were caused by fluorine. This seems possible, for minor dystrophies are known to result from constitutional disturbances, and it would account for reports of widespread "dental fluorosis" in unexpected areas.

Most of the knowledge gained has come from the examination of children, but Deatherage (1943) and McKay (1948) produced evidence that caries resistance once acquired may be permanent. McKay's findings are illustrated in fig. 2 taken from Dean (1949). His figures were based upon the examination of 400 adult residents at Colorado Springs where natural water with a mean annual fluorine content of 2·5 p.p.m. had been drunk for the past seventy years. Russel and Elvove (1951) also showed that the caries-rates for adults in each age-group in Colorado Springs were about 60% lower than in Boulder, where the water is practically fluorine-free. This figure was maintained up to the age of forty-four, but mottled enamel was almost universal in Colorado Springs.

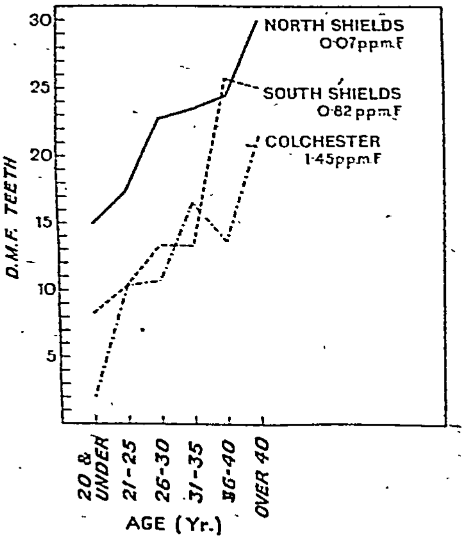


Fig. 3—Decayed, missing, or filled teeth at North Shields, South Shields, and Colchester.

Weaver (1948) thought that the resistance of children in South Shields diminished during adult life, when the greatest benefit to be expected was a deferment of the onset of caries by three to five years, but Forrest et al. (1951) found that a high degree of immunity persisted into adult life. This survey was described somewhat modestly by the authors as a pilot survey, evidently because the numbers examined were comparatively small. The reduction in the number of decayed, filled, and missing teeth in people taking high-fluorine water varied from a maximum of 38% at twenty-one to twenty-five years of age to a minimum of 16% at thirty-six to forty years and 17% at over forty (fig. 3). The investigators considered that the lower incidence in adults in the high-fluorine areas was equivalent to a delay of ten years in the onset of caries. They noted also that caries was more severe in the low-fluorine group, and that, of those teeth which were present and decayed, 12 times as many showed apical infection. There was no severe mottling or pigmentation among 268 mothers in the high-fluorine areas, and in the few cases where mottling existed it could be detected only by careful clinical examination, despite the fact that 79 mothers received a water-supply containing 1·45 p.p.m. of fluorine. These observations agree closely with those of similar surveys in the U.S.A. Forrest et al. also found an inverse proportion between fluorine and dental caries in the three low-fluorine areas in which the concentrations were 0·07, 0·1, and 0·3 p.p.m. (fig. 4). This suggests that some benefit may be derived even at such low levels, which is in keeping with the relationship plotted by Dean (fig. 1).

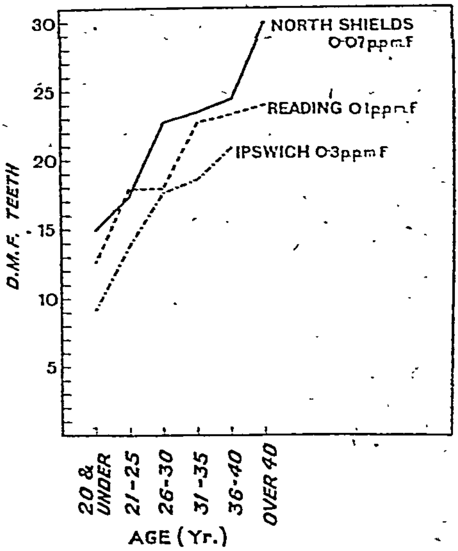


Fig. 4—Decayed, missing, or filled teeth at North Shields, Reading, and Ipswich.

EXPERIMENTAL ADDITION OF FLUORINE TO PUBLIC WATER-SUPPLIES

The first large-scale experiment in prevention began at Grand Rapids, Michigan, in January, 1945, and later in the same year at Newburgh, New York, and Brantford, Ontario. The full results will not be known until they have been in progress for fifteen years or more—i.e., until the permanent teeth of children born since 1945 have erupted and been exposed for sufficiently long to the influences that cause decay. Nevertheless, the preliminary results leave little doubt that the protection given by naturally occurring fluorine is also conferred by waters to which it has been artificially added.

It will be sufficient to study the first two such experiments, the results of which are being reproduced elsewhere.

There is no reason to doubt the accuracy of measurements of fluorine intake, but estimations of the point of equilibrium between intake and output are less reliable. Excretion of fluorine in the sweat (McClure et al. 1945) has sometimes been disregarded. This is no more than a possible explanation of some discrepancies between biochemical determinations and the results of field surveys of large populations. For example, an intake of 2·2 mg. per day is almost exactly what would be expected if drinking-water contained 1·3 p.p.m. and food 0·3 p.p.m. —levels at which they have been taken without harm by probably over 1,000,000 Americans. The conclusion is therefore unavoidable that in such amounts fluorine is non-toxic.

The poisonous nature of fluorine should be recognised, but it should equally be recognised that it is consumed daily in non-toxic doses by everybody as a natural constituent of nearly all foods and many waters, and there is no evidence whatever that it is in any way harmful in the doses required for the prevention of dental caries. There is far more evidence to support this contention than there is to justify many of the large number of drugs, accessory food factors, and other dietary substances now freely obtainable and widely used.

POSSIBLE EFFECTS OF FLUORINE UPON INDUSTRY

The addition of fluorine in the quantities proposed has no effect upon the taste, odour, colour, or acceptability of water for domestic use. It may affect boiler-feed water and zeolites used for water-softening, but this can easily be counteracted if necessary. No serious industrial consequences have been reported from areas having natural high-fluorine waters. Fluorine may inhibit bacterial and enzymatic processes, and its possible effect in industries depending upon them—e.g., brewing and distilling—should not be overlooked.

VARIATIONS IN INTAKE OF FLUORINE

Objections may be raised that a fixed dose of fluorine in the water-supply will ensure the optimum intake only to the average person. The variations of fluid intake with the physiological characteristics of individuals and with their mode of life cannot be eliminated. I do not think that it has ever been suggested that such variations may be responsible for the mild dental fluorosis which has often been noted in a small proportion of the population when the level of fluorine is such as to cause no symptoms in the majority.

Another consideration is the effect of climate on fluid intake. More information about the importance of atmospheric temperature and relative humidity is needed before the dosage can be regulated to counteract such effects. Maier (1950) suggested that where the mean annual temperature exceeds 55°–60°F the water should contain less than 1 p.p.m. of fluorine, and at Charlotte, North Carolina, an attempt has been made to correlate mean monthly temperatures, water intake, and fluoride level (fig. 7).

It might be an advantage, even in our comparatively equable climate, to have some slight seasonal variations in dosage, but there has been no such variation in the waters naturally containing fluorine or in the majority of those to which it has been added. The results of using these waters on a large scale must determine whether or not it is desirable to supplement the fluorine content of a public water-supply. Great benefits may be secured without refinements in dosage, although, when established upon the sound basis of experience, these may lead to increased efficiency and to economy of materials.

OTHER METHODS OF ADMINISTERING FLUORINE

It has often been suggested that the benefits of fluorine could and should be obtained by giving it otherwise than in water. Pills and tablets, local application to the teeth, and the incorporation of a fluoride in table salt or chewing-gum have been advocated. But these methods might involve errors in dosage much greater than could occur when it is given in solution, though overdoses large enough to cause danger to health are unlikely. The work of Dean et al. (1934) and McClure et al. (1945) indicated that absorption of fluorine in solid form may be less than when it is taken in water, and there is no reliable guide to the optimum dose as there is when it is in solution. Pills might be given to school-children—but it would be difficult to make sure that they took them. Moreover it is very important that children under school age should also be included. The use of table salt as a vehicle would be no more successful because salt is not regularly given in infancy. Many years of research on a large scale would be required before the correct dose for such methods could be ascertained.

Stones et al. (1949) found that fluorine in solid form by mouth did not give the results hoped for. In one group of children there appeared to be some increased resistance, but in other groups where ingestion was combined with topical application there was no such resistance.

McClure (1949) found that a fluoride given to cows had no effect upon the milk. McClendon et al. (1943) showed that caries in school-children varied inversely with the fluorine content of the milk they drank, and it has been suggested that milk might be used as a vehicle. But here again the intake would vary greatly and the fortifying of milk in this way would hardly be practicable. Moreover, the deciduous teeth and possibly the permanent teeth may be influenced during breast-feeding, and it may be just as important that the expectant mother should have an adequate intake of fluorine. I have, however, been unable to find records of any observations on the fluorine content of breast-milk in high and low fluorine areas. Such an investigation would be an important contribution to our knowledge.

McClure (1949) found that tea-leaves, bone-meal, and fish contain relatively high, though variable, proportions of fluorine. A low susceptibility to caries has been noted in the inhabitants of Tristan da Cunha whose diet contains much fish. There is nothing to show that heavy tea-drinkers have a similar resistance, although a high proportion of the fluorine passes into solution when tea is brewed. In any case control of fluorine consumption in either of these ways would be impracticable.

Bibby (1945) reported no reduction in caries when fluorine was added to dentifrices. Chewing-gum containing fluorine might not be popular with some parents in this country.

Knutson and Armstrong (1943, 1945, 1946) applied a 2% solution of sodium fluoride to the scaled and polished teeth of children. Seven to fifteen applications were made at weekly intervals and the results compared with a control group. The number of permanent teeth attacked by caries for the first time was 36·7% less after three years than in untreated teeth. Teeth which were carious at the start showed less extension of the damage in the treated children than in the controls.

Galagan and Knutson (1947) found that the protection increased with the number of applications up to four at weekly intervals after which no further protection was given.

Stones et al. (1949) found that eight applications of a 2% solution of potassium fluoride at three-monthly intervals for two years gave little or no benefit, but no mention is made of the teeth being scaled and polished which is an important preliminary (Knutson et al. 1947).

Local application cannot be summarily dismissed, but the preparatory scaling and polishing, upon which success seems to depend, may be beyond the capacity of an already overburdened dental service. Moreover, it is not yet certain that the reduction in caries would justify the method which could, however, be used in places where it is difficult to treat the water-supply.

With increasing knowledge, some alternative to the public water-supply may be found, but to await the outcome of researches, which must necessarily be long, would deprive the public of benefits which they might receive almost immediately.

ESTIMATION OF FLUORINE

The standard zirconium-alizarin colorimetric or Scott-Sanchis method (as modified by Lamar 1945) is recommended by Maier (1950).

This method was used by Forrest et al. (1951) and the results were checked by the somewhat laborious and complicated distillation process (Willard and Winter 1933, Hoskins and Ferris 1936). There was close agreement between the two methods.

If the water is coloured or if interfering substances are present beyond certain limits the distillation method must be used.

THE DOSE OF FLUORINE

Precise control of dosage is necessary if the highest degree of protection is to be given without risk of unpleasant mottling of the enamel. Ample guidance on this point is available from the American experiments. Types of apparatus in common use have been described by Bull et al. (1951) and Harper (1951).

The fluoride ion has been added to water-supplies as sodium fluoride, sodium fluosilicate, and, once or twice for special reasons, as fluosilicic acid and hydrofluoric acid. Feeders for both solutions and solids have been developed from apparatus used in adding chemicals for water purification. There is no doubt that dosage can be maintained well within the limit of the 5% error officially permitted in the U.S.A.

Adequate facilities for treatment and supervision are more difficult to provide where water is drawn from wells, but such difficulties have been overcome in the U.S.A. Uncontrolled use of fluorine would expose the operators to a hazard; but complete protection against the dangers of inhaling sodium fluoride and sodium fluosilicate dust (Roholm 1937) have been provided in other industries, and this risk is no objection.

The American Water Works Association (1949) has suggested a plan which provides for controlled dosage, laboratory analysis and control, testing for purity of the chemicals used, the protection of operators from the industrial hazards, and the sharing of the cost by the water companies and the public health and other authorities. It does not specifically provide for the automatic metering of the water and the recording of the rate of delivery of the chemical, which I consider desirable or even essential, but the latter is usually achieved in gravimetric loss-in-weight dry-feeders by a built-in mechanism. The rate of delivery can be automatically adjusted to changes in the flow of water past the treatment point, and this also is desirable, though not essential.

The recording of the volume of water treated, the weight of chemicals used, and the results of regular estimations of the fluorine passing into the supply should be compulsory, and such records should be available for inspection by the health authority. With such precautions there could be no possibility of harm.

THE COST OF FLUORIDATION

The American Water Works Association (1949) estimated that the total cost of fluoridation, including capital interest, depreciation, operating costs, and laboratory control, lay between 5 and 15 cents (about *4d.* to *1s.*) per consumer per year. A quotation from a chemical manufacturer in this country shows that prices for fluorine preparations are much the same as those in the U.S.A. Since consumption of water per head in the U.S.A. is more than twice that in this country, our cost per consumer might well be less. This cost should be offset many times by savings in the cost of the dental service and by the relief of much suffering and inconvenience. This adequately answers the charge that the use of the public water-supply involves unjustifiable extravagance because only a very small proportion of water is used for drinking whereas all must be treated. It would seem to be not so much a question of whether we can afford fluoridation but rather of whether we can afford to do without it.

DISCUSSION

There is ample proof that the addition of fluorine to a water-supply deficient in that element will reduce the incidence of dental caries in children. There is also good reason to believe that substantial benefit will persist in adult life. There is, however, some disagreement about how much benefit may be expected. The previous dental health of the community must clearly influence results and be an important consideration in deciding policy. The records of the national dental service may help to assess this point.

The way in which the benefits of fluorine should be recorded is also disputed. In America it has been usual to base this upon the difference in D.M.F. teeth in two similar communities or in the same community before and after fluoridation. This method has been criticised by Weaver who thinks it more accurate to express the lowered incidence in terms of the delay in the onset of caries. Another factor, which is not adequately accounted for by either method, is the reduction in apical infection and in the severity of caries (Forrest et al. 1951). Moreover, the D.M.F.-rate gives no indication of the severity of the disease in any particular tooth; a missing tooth or one which is diseased beyond repair carries the same weight as one with the smallest cavity. Such differences might, of course, be the result of conservative treatment in the past, but they might on the other hand give a false impression when benefit is assessed by deferment of caries.

The innocuous nature of fluorine in concentrations which will reduce caries has been definitely proved. Experiences in this country may be more convincing than similar but more extensive evidence from the U.S.A. The water at West Hartlepool naturally contains 2·0 p.p.m. of fluorine and that at Maldon contains about 5·0 p.p.m. Adults who have arrived in these towns since the calcification of their permanent teeth have drunk water containing 2–5 times the proposed concentration with no ill effect and without knowing that they were doing so. Children reared in these two towns have suffered no consequences other than varying degrees of mottled enamel; but at South Shields, where the concentration is close to that proposed (1·0 p.p.m.), the reduction in caries has not been accompanied by noticeable mottling.

At Maldon it is obviously desirable that the fluorine content of the water should be reduced to prevent the disfigurement of mottled enamel. But could it seriously be argued that all the fluorine be removed and that mottling be replaced by increased dental decay? I submit that such a procedure would be unthinkable and that fluorine should be reduced to no less than 1·0 p.p.m. This simple problem perhaps best illustrates the soundness of controlled fluoridation of public water-supplies.

The waterworks industry in this country has never hesitated to institute any measure that the health authority has considered valuable. It cannot itself assess the value of fluoridation, but if the health authority decides that this will contribute to better health, then I do not doubt that the industry will be eager to put the plan into practice, provided it is satisfied that it is not otherwise undesirable.

There are, however, other matters that must receive consideration. First among these are the ethics of mass experiments on a civil population. Some regard these as wrong—an impression fortified by the unfortunate description "mass medication." But to add fluorine to water under controlled conditions is only to supplement the intake of an element, naturally present in many foods and often in water, in order to encourage the development of a more serviceable kind of dental enamel which Nature doubtless intended we should have. It is not unethical nor is it in any way less desirable than improving our flour by adding calcium, or our margarine by adding vitamins—measures instituted with official sanction and widely welcomed by informed opinion.

I consider, firstly, that the American experiments were justified by the fact that many people consumed throughout their lives water containing fluorine in the concentrations used without harmful effect, and in concentrations many times higher with no more serious effect than varying degrees of mottled enamel. Secondly, constitutional effects can develop only by cumulative action over a long period and in a controlled experiment they could be detected early and the addition of fluorine stopped or reduced before serious consequences arose. In the case of radioactive elements in water it is not so easy to bring the situation under control in good time, for the damage may not be recognised until too late and may even be handed down to succeeding generations. Yet the discharge of radioactive elements into waters used for domestic supply has been officially sanctioned, and has been announced in the press without noticeable protest. I do not suggest that this endangers the health of consumers, for adequate control has been ensured. My point is simply that this has been permitted, not to benefit the people, but as a matter of convenience. How much greater is the justification for adding to water a relatively innocuous substance which will improve health?

It is too early to measure in full the benefits of fluoridation. From eight to fifteen years have been said to be the shortest time that must elapse before full assessment is possible. The earliest experiments have now been studied for six years, and expectations have been fulfilled.

Would the endorsement of fluoridation by the water industry create a precedent for all sorts of additions? My answer is that provided the supreme health authority had satisfied itself by sufficient scientific evidence that the people would benefit, there is no reason why this should not be done. We add lime to acid water to preserve our pipes from corrosion. If it had been shown that a similar addition would enable us to build stronger bones and better teeth, or otherwise to enjoy better health, what would be the objection? Fluorine, if added under the conditions that have been outlined, is no more objectionable than lime.

There would, of course, be an outcry from a small and for the most part uninformed minority. In Charlotte, North Carolina, it was announced that fluoridation was to begin on April 1, 1949. Immediately after the appointed day complaints were received attributing to fluorine such things as unpleasant tastes, ruined photographic films, stained clothing, and the death of goldfish. But fluoridation had been deliberately withheld, and when this was announced the complaints ceased. When fluoridation was started on April 25, *without announcement*, no complaints were received.

The relatively high fluorine content of certain teas has been mentioned, and it might be argued that our knowledge of the rôle of tea in providing available fluorine [illegible] that an otherwise desirable measure [illegible] until further researches have been made. *To this I would reply that*, in preventive medicine, if we had always waited for complete knowledge, we should have advanced little beyond the state of the Middle Ages. Moreover, tea consumption is insufficient to cause symptoms of fluorosis other than mottled enamel, which can be produced only during calcification of the teeth and therefore at an age when the consumption of tea is least. There is no reason to believe that the people of South Shields drink less tea than those elsewhere in England, yet the fluorine content of their water has improved their dental health to almost exactly the extent expected from experience with similar waters in the U.S.A., and there have been no undesirable consequences.

I have tried to present impartially the evidence for and against the fluoridation of public water-supplies. We are justified in believing that it is possible substantially to reduce the incidence of dental caries without any undesirable effects. The fluorine content of water which confers the greatest benefit without harm is known and can be maintained with great accuracy by established *methods of dosing. Other vehicles for fluorine have been* tested and have all been found wanting. The cost is relatively unimportant. Thus my six introductory questions have been satisfactorily answered.

Where does the matter now stand in this country? The survey by Forrest et al. (1951) was described as a pilot investigation suggesting that it will lead to more extensive surveys. *It is to be hoped that these will not* follow the path already explored in the U.S.A. They should try to solve instead certain problems, some of which have been mentioned, where knowledge is scanty and information often contradictory. Fluoridation need not be postponed until such work has been done; further experiments at this late stage would mean another delay of from eight to fifteen years.

The public is almost completely ignorant of, or quite indifferent to, the benefits that may come from fluoridation. Many of those who are responsible for the provision of public water-supplies know the facts and await a directive from the highest medical authority, by whom the policy should be decided.

We in this country are wisely conservative about such matters, but it should not be forgotten that any delay means damage to children's teeth which cannot be undone. Some delay will be inevitable, but the intervening period need not be wasted, for there is much ground to be prepared. The formation of a code of practice alone will take time; education is required and administrative procedure must be settled, to mention only a few of the necessary preparations. What is to be feared is unnecessary delay due to the hope of some better method being found.

I do not wish *it to be thought that I am advocating the irresponsible addition of* fluorine to public water-supplies. A strict code of practice should be *laid down* governing the quantity of fluorine to be *given and the* methods of application and laboratory control. No water undertaking should be permitted to add fluorine until its plans have been approved by the central health *authority*.

The American Public Health Association (1951), reporting that a single manufacturer had installed 62 fluoridation plants in the U.S.A., asked "What are the rest of us waiting for?" The same question might well be asked, and indeed is being asked, in this country today.

SUMMARY

Waters with a high fluorine content are responsible for the dental dystrophy known as mottled enamel, and also for an increased resistance to dental caries.

People who have throughout their lives drunk water with a natural fluorine content of 1·0 p.p.m. or more have substantially less dental caries than those whose water-supply *is practically fluorine-free. Strong evidence* suggests that this benefit can be given without unsightly mottling of the enamel.

The preliminary results of large-scale experiments in fluoridation support this conclusion. In the U.S.A. 1,700,000 people are now drinking water the fluorine content of which has been artificially increased to not *less than 1·0 p.p.m.*

The toxicity of fluorine at a concentration of 1 p.p.m. is insufficient to give trouble, and dosage can be accurately controlled.

The cost of a fluoridation scheme is estimated at from *4d.* to 1*s.* per consumer per year.

Alternative methods of giving fluorine are unsatisfactory.

Further experiments are unnecessary and would only delay the substantial benefits which can be expected from fluoridation of water-supplies in this country.

REFERENCES

Ainsworth, N. J. (1928) *Roy. dent. Hosp. Mag.* 2, 2.
— (1933) *Brit. dent. J.* 55, 233.
— (1934) *Analyst*, 59, 380.
American Dental Association (1950) News release. Aug. 1.
American Public Health Association (1951) *Amer. J. publ. Hlth*, 41, 224.
American Water Works Association (1946) *J. Amer. Wat. Wks. Ass.* 38, 361.
— (1949) *Ibid*, 41, 575.
— (1951) *Ibid*, 43, 602.
Armstrong, W. D. (1937) *J. biol. Chem.* 119; *Sci. Proc.* 31, 5.
Ast, D. B., Finn, S. B., Chase, H. C. (1951) *J. Amer. dent. Ass.* 42, 188.
Bibby, B. G. (1945) *J. dent. Res.* 24, 297.
Black, G. V., McKay, F. S. (1916) *Dent. Cosmos.* 58, 129.
Bromehead, C. N., Murray, M. M., Wilson, D. C. (1943) *Lancet*, i, 490.
Bull, F. A., Hardgrove, T. A., Frisch, J. G. (1951) *J. Amer. dent. Ass.* 42, 29.
Clifford, W. M. (1925) *Biochem. J.* 19, 218.
Cox, C. R., Ast, D. B. (1951) *J. Amer. Wat. Wks. Ass.* 43, 641.
Cox, G. J., Hodge, H. C. (1950) *J. Amer. dent. Ass.* 40, 440.
Crichton-Browne, J. (1892) *Lancet*, ii, 6.
Dean, H. T. (1933) *Publ. Hlth Rep., Wash.* 48, 703.
— Sebrell, W. H., Breaux, R. P., Elvove, E. (1934) *Ibid*, 49, 1075.
— Dixon, R. M., Cohen, C. (1935) *Ibid*, 50, 424.
— Elvove, E. (1935) *Ibid*, p. 1719.
— — (1937) *Ibid*, 52, 1249.
— (1938) *Ibid*, 53, 1443.
— Jay, P., Arnold, F. A. jun., McClure, F. J., Elvove, E. (1939) *Ibid*, 54, 862.
— (1940) *J. Pediat.* 16, 782.
— Jay, P., Arnold, F. A. jun., Elvove, E. (1941) *Publ. Hlth. Rep., Wash.* 56, 761.
— Arnold, F. A. jun., Elvove, E. (1942) *Ibid*, 57, 1155.
— (1949) *Postgrad. med. J.* 5, 361.
— Arnold, F. A. jun., Jay, P., Knutson, J. W. (1950) *Publ. Hlth Rep., Wash.* 64, 1403.
Deatherage, C. F. (1943) *J. dent. Res.* 22, 129, 173.
Forrest, J. R., Parfitt, G. J., Bransby, E. R (1951) *Mon. Bull. Min. Hlth*, 10, 104.
Galagan, D. J., Knutson, J. W. (1947) *Publ. Hlth Rep., Wash.* 62, 1477.
Harper, L. E. (1951) *J. Amer. Wat. Wks. Ass.* 43, 744.
Hill, I. N., Jelinek, O. E., Blayney, J. R. (1949) *J. dent. Res.* 28, 398.
Hoskins, W. M., Ferris, C. A. (1936) *Industr. Engng Chem.* 8, 6.
Kempf, G. A., McKay, F. S. (1930) *Publ. Hlth Rep., Wash.* 45, 2923.
Knutson, J. W., Armstrong, W. D. (1943) *Ibid*, 58, 1701.
— — (1945) *Ibid.* 60, 1085.
— — (1946) *Ibid.* 61, 1683.
— — Feldman, F. M. (1947) *Ibid.* 62, 425.
Lamar, W. L. (1945) *Industr. Engng Chem.* 17, 148.
McClendon, J. F., Foster, W. C., Supplee, G. C. (1943) *Arch. Biochem.* 1, 51.
McClure, F. J., Mitchell, H. H. (1931) *J. biol. Chem.* 90, 297.
— (1933) *Physiol. Rev.* 13, 277.
— Mitchell, H. H., Hamilton, T. S., Kinser, C. A. (1945) *J. industr. Hyg.* 27, 159.
— (1948) *J. dent. Res.* 27, 287.
— (1949) *Publ. Hlth Rep., Wash.* 64, 1061.
McCollum, E. V., Simmonds, N., Becker, J. E. (1925) *J. biol. Chem.* 63, 553.
Machle, W., Scott, E. W., Treon, J. (1939) *Amer. J. Hyg.* 29, 139.
— — Largent, E. J. (1942) *J. industr. Hyg.* 24, 199.
McKay, F. S. (1918) *J. nat. dent. Ass., Huntington, Ind.* 5, 721.
— (1948) *Amer. J. publ. Hlth*, 38, 6.
Maier, F. J. (1950) *J. Amer. Wat. Wks. Ass.* 42, 1120.
Medical Research Council (1949) Industrial Fluorosis. Memo-no. 22. H.M. Stationery Office.
Mellanby, M., Mellanby, H. (1952) *Brit. med. J.* i, 7.
Ockerse, T. (1941) *S. Afr. med. J.* 15, 261.
Panditt, C. G., Raghavachari, T. N. S., Rao, D. S., Krishnamurti, V. (1940) *Indian J. med. Res.* 28, 533.
Parfitt, G. J. (1951) *Postgrad. med. J.* 27, 349.
Roholm, K. (1936) See *Bull. Hyg., Lond.* 1937, 12, 20.
— (1937) Fluorine Intoxication. London.
Russel, A. L., Elvove, E. (1951) *Publ. Hlth Rep., Wash.* 66, 1389.
Schlesinger, E. R., Overton, D. E., Chase, H. C. (1950) *Amer. J. publ. Hlth.* 40, 725.
Shortt, H. E., Panditt, C. G., Raghavachari, T. N. S. (1937a) *Indian med. Gaz.* 72, 396.
— MacRobert, G. R., Barnard, T. W., Nayar, A. S. M. (1937b), *Indian J. med. Res.* 25, 553.
Spira, L. (1942) *Lancet*, i, 649.
Stones, H. H., Lawton, F. E., Bransby, E. R., Hartley, H. O. (1949) *Brit. dent. J.* 86, 263.
Weaver, R. (1944) *Ibid.* 76, 29.
— (1948) *Proc. R. Soc. Med.* 41, 284.
— (1950) *Brit. dent. J.* 88, 231.
Willard, H. H., Winter, O. B. (1933) *Industr. Engng Chem.* 5, 7.

PROVINCIAL TEACHING HOSPITALS

Boards of Governors

THE Minister of Health has made the following appointments, to fill vacancies caused by the retirement of a third of the members, to the boards of governors of the ten provincial teaching hospitals in England and Wales. Of the 101 appointments, 75 are reappointments of retiring members. The names of medical members are shown in bold type. Those now appointed will hold office till March 31, 1955.

UNITED NEWCASTLE-UPON TYNE HOSPITALS

Reappointed: **T. H. Bates,** M.D. J.P.; Norleigh Booth; W. D. Lockey, J.P.; **S. W. Davidson,** F.R.C.P., F.F.R.; N. Garrow, J.P.; **John Gilmour,** F.R.C.S.; Sir Mark Hodgson, O.B.E., J.P.; Mrs. E. W. Mitchell; Sir **James Spence,** M.C., F.R.C.P.

New members: John Horsley; C. I. C. Bosanquet, M.A., and T. C. Squance, O.B.E., D.L., J.P. (till March 31, 1954).

UNITED LEEDS HOSPITALS

Reappointed: Alderman H. J. Bambridge, O.B.E., J.P.; J. W. Booth; F. J. Higginson; **J. T. Ingram,** F.R.C.P.; C. R. Morris; **L. N. Pyrah,** F.R.C.S.; H. A. Ryott; Mark Whittock.

New member: Prof. **R. E. Tunbridge,** F.R.C.P.

UNITED SHEFFIELD HOSPITALS

Reappointed: E. A. Barker; Sir Basil Gibson, J.P.; **W. J. Lytle,** F.R.C.S.; **J. G. McCrie,** O.B.E., F.R.C.P.E.; Prof. **G. L. Roberts,** M.B., F.D.S. R.C.S.; Prof. **C. H. Stuart-Harris,** F.R.C.P.; Alderman Mrs. Grace Tebbutt; J. W. Trickett, J.P.

UNITED CAMBRIDGE HOSPITALS

Reappointed: S. O. Chivers; **Leslie Cole,** F.R.C.P.; P. F. Dennard; **Robert Ellis,** M.D.; E. J. Harding; S. G. Newman; **Vernon Pennell,** F.R.C.S.; A. L. Symonds; Sir **Lionel Whitby,** F.R.C.P. One appointment outstanding.

UNITED OXFORD HOSPITALS

Reappointed: L. B. G. Bellinger; Sir **Hugh Cairns,** F.R.C.S.; **A. M. Cooke,** F.R.C.P.; H. A. Goddard; G. E. C. Holt; Alderman Lady Townsend, J.P.; Prof. **L. J. Witts,** F.R.C.P.

New members: Sir George Schuster, K.C.S.I., K.C.M.G., C.B.E., M.C.; Councillor C. A. Cooke, M.A., LL.D.

UNITED BRISTOL HOSPITALS

Reappointed: Egbert Cadbury, D.S.C., D.F.C., M.A., D.L., J.P.; Prof. **R. H. Parry,** F.R.C.P.; Prof. **C. Bruce Perry,** F.R.C.P.; H. G. Tanner, J.P.; **J. H. Grove-White,** M.D.

New members: **A. L. Eyre-Brook,** F.R.C.S.; A. E. Haynes; H. L. Shepherd; Gordon Simpson.

UNITED CARDIFF HOSPITALS

Reappointed: Sir Frederick Alban, C.B.E., J.P.; Councillor Helena Evans; Prof. **Jethro Gough,** M.D.; Prof. **R. M. F. Picken,** C.B.E., M.B.; C. J. Hardwick; W. R. Jeffcott; **Lewis Lewis,** M.B.

New members: **R. G. Maliphant,** F.R.C.O.G.; J. C. Radcliffe; Alderman D. T. Williams.

UNITED BIRMINGHAM HOSPITALS

Reappointed: **A. Beauchamp,** M.B.; C. A. F. Hastilow, O.B.E., F.R.I.C.A.; K. Mindelsohn; Mrs. H. Murtagh; T. Patterson; **B. T. Rose,** F.R.C.S.; Mrs. R. J. Smith; Prof. **C. F. V. Smout,** M.D.; Prof. **A. P. Thomson,** F.R.C.P.

New member: L. Whitehouse.

UNITED MANCHESTER HOSPITALS

Reappointed: N. M. Agnew; **William Chadwick,** M.B.; S. H. Hampson; K. G. Holden; **R. L. Newell,** F.R.C.S.; William Onions; Prof. **Robert Platt,** F.R.C.P.

New members: **K. V. Bailey,** F.R.C.O.G.; **R. W. Fairbrother,** F.R.C.P.; Rt. Rev. J. L. Wilson, C.M.G.; L. G. M. Crick, E. C. Sumner, J.P., and Prof. W. Mansfield Cooper, LL.M. (till March 31, 1953).

UNITED LIVERPOOL HOSPITALS

Reappointed: Mrs. Elizabeth Braddock, M.P.; **T. A. Jermy,** M.B.; J. F. Mountford; Sir John Nicholson; Councillor David Nickson; Alma Parkin, J.P.

New members: **R. W. Brookfield,** F.R.C.P.; J. Hamilton, J.P.; **J. M. Leggate,** F.R.C.S.; **J. B. Oldham,** F.R.C.S.; W. L. Blease, LL.M.; Richard Davies (till March 31, 1953).

Medical Conferences

THE NATURE OF VIRUS MULTIPLICATION

The spring congress of the Society for General Microbiology was held at Oxford, the theme for the discussions being the Nature of Virus Multiplication. The symposium fell into two main parts, the first being a discussion of the general principles involved in the production of virus material, and the second a discussion of the means of reproduction in specific viruses.

FORMATION OF VIRUS MATERIAL

New virus material is nucleoprotein in nature, and H. **Chantrenne** pointed out that the processes of its formation were intimately linked with the ribosonucleic acids of the cell cytoplasm and with the high-energy phosphate bonds of adenosine triphosphate. The real difficulty, he said, was to explain how a specific protein was created: to state that this was due to enzymic action was begging the question, since each enzyme would be protein in nature and require another set of enzymes to build it up. Two possible mechanisms might account for protein specificity; one was the template theory put forward by Pauling,[1] and the other (Chantrenne suggested) was that unwanted material was broken down by cell proteases, in which case the nucleoproteins produced in a cell might be those that were capable of withstanding the intracellular proteolytic enzymes. F. C. **Bawden** and N. W. **Pirie** suggested that the specificity of nucleoproteins produced as a result of virus infections in plants was less exact than many virus workers believe, and that at least 99% of the proteins produced as a result of infection were serologically identical with the virus but were non-infective. The only character which differentiated a virus from any other nucleoprotein was its ability to infect a cell, and, this being so, the so-called "soluble" phases of viruses should be treated with much reserve as many such stages were most probably by-products of virus multiplication.

Both these speakers and those who followed emphasised that the great difference between viruses and bacteria lay in their dependence on the host-cell for multiplication, which implies that it may be much more difficult to find criteria which enable us to differentiate between viruses and cell nucleoprotein than it is to find differences between bacteria and virus. Until such characters are found, many viruses will remain unrecognised; for all viruses do not possess the essential feature of pathogenicity which at the present time enables us to recognise them.

Other problems discussed included the part played by nucleic acids in the synthesis of new virus particles, and it was thought that these compounds have as great a potential specificity as has the protein moiety of the virus particle. R. **Markham**, working with plant viruses, has shown that at least six and possibly thirty nucleic acids may be present in a virus particle, and he suggested that they may be responsible for the characters of the virus, the protein portion acting as a carrier for these nucleic acids.

A discussion on the enzymic activity of viruses showed that there are two schools of thought; one believes that the agglutination of erythrocytes by influenza virus is enzymic, while the other thinks that viruses are without enzymes. Whichever view is correct it has been established that viruses are without respiratory activity and do not possess enzymes which would enable them to reproduce.

MULTIPLICATION OF VIRUSES

From the discussion of the general problems of virus multiplication it could be concluded that the virus metabolism is so intimately linked to the cell that the formation of the fresh virus particles is probably by the same pathways which the cell uses to reproduce its own nucleoproteins, and only in the matter of "specificity" does the virus material differ. How virus "specificity" of the protein and nucleic acids is established in the cell is as yet unknown, and though the template theory has great theoretical attractions its application to individual problems is more difficult.

Further discussion took place on the multiplication of individual viruses, and the most argument centred around influenza virus and the [illegible] use these viruses are readily hand[illegible] methods can be used in their study. In both these types of organism the most interesting problem is the question of the changes which occur between the infection of a cell and the appearance of fresh virus within the cell. During this latent period no infective virus can be found within the cell. A few years ago Luria[2] suggested that the phage breaks up into units which reproduce individually and then re-aggregate to form the infective particle, but recently Dulbecco[3] has shown, by radiation studies of infected cells, that this is not the explanation and Luria has abandoned his earlier views. At the present time no explanation accounts for all the phenomena observed in the bacterial viruses; this might be due, as Felix[4] believes, to the fact that bacteriophages are not a virus but are a part of the bacterial cell with a separate existence.

No discussion of bacteriophage multiplication would be complete without a consideration of how lysogenic bacterial strains are formed; and here again there were two schools of thought, the one believing in Lwoff's[5] theory of the prophage, and the other accepting Boyd's[6] view that bacteria are lysogenic because they carry non-pathogenic or symbiotic bacteriophage particles. The discussion on these lysogenic bacteria suggested that bacteriophage may infect bacteria and give rise to a lysogenic strain of organisms in more than one way.

The reproduction of influenza virus has been studied in much detail, and with this and other animal viruses discussion turned largely on the nature of the latent period after infection and Hoyle's[7] theory that the virus is built up in a series of differing units which aggregate to form the influenza elementary body. Hoyle bases his views on the serological differentiation of the various units of the particle, but this opinion was strongly criticised. It was suggested that his results could be explained if influenza produced non-infective serologically specific material, as has been found in plant viruses. In support of the view von Magnus[8] has shown that "incomplete" or non-infective material can be produced by influenza virus. Those who disagreed with Hoyle's theory argued that there is no need to assume a break-up into separate units; they thought that the viruses could multiply by each genetic unit of the virus reproducing itself and so forming a new particle. As in the case of bacteriophages, no theory quite explains the facts observed; the objections to Hoyle's theory have already been stated, and any theory which insists on a simple replication and fission of virus particles does not adequately account for the latent period or the recombination of viruses observed by Burnett.[9]

While much more information is available for bacteriophages and influenza viruses, the problem is being investigated with other viruses; but in many of these investigations the results are complicated by the fact that it is necessary to use animal hosts, making it difficult to have a detailed analysis of each step as is possible with bacteriophages.

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[1] Pauling, L. *J. Amer. chem. Soc.* 1940, 62, 2643.

[2] Luria, S. E. *Proc. nat. Acad. Sci., Wash.* 1947, 33, 253.

[3] Dulbecco, R. *J. Bact.* 1952, 63, 199.

[4] Felix, A. Proc. 4th International Congress of Microbiology, 1947, p. 355.

[5] Lwoff, A., Gutmann, A. *Ann. Inst. Pasteur,* 1950, 78, 711.

[6] Boyd, J. S. K. *J. Path. Bact.* 1951, 63, 445.

[7] Hoyle, L. *Brit. J. exp. Path.* 1948, 29, 390.

[8] von Magnus, P. *Acta path. microbiol. scand.* 1951, 29, 157.

[9] Burnett, F. M., Lind, P. E. *J. gen. Microbiol.* 1951, 5, 59.

If one may generalise—and in such a diverse group of organisms it is possibly unwise to do so—it seems there are three main steps in virus multiplication. The first step is the entry of the virus into a susceptible cell and its loss of infectious form; the second is the period between infection and the appearance of fresh infective virus; and the third is the increase in number and maturation of the virus particles leading to the disorganisation of the host cell. In the solution of the second of these problems may lie the clue to the nature of life.

C. H. S.

Parliament

Third Reading of the N.H.S. Bill

On the motion for the third reading, Miss PATRICIA HORNSBY-SMITH, parliamentary secretary to the Ministry of Health, said that the Government had not introduced the Bill for the sheer delight of taking the National Health Service to pieces, but because they had to take a realistic view of the country's financial difficulties. They regretted the necessity for this Bill, but they were called upon to cure the financial fever of their predecessors. Having decided to implement the 1949 Act and impose a shilling prescription charge, the Government had introduced this tidying-up measure so that there should be no anomaly between patients obtaining prescriptions from their general medical practitioners and taking them to chemists, and other patients going to the outpatient and dispensing departments of hospitals. Such an anomaly would have increased the pressure on the outpatient departments.

In committee, Miss Hornsby-Smith continued, they had been pressed to make exemption from these payments for various types of ailment and patient. An amendment had been passed exempting patients with venereal disease. This was a clearly defined group of patients who were treated at special centres. We were also bound by the Brussels Agreement. But this was the only exemption they were prepared to make. Exemptions made according to the nature of the ailment would make it difficult for the hospitals to administer the scheme. Exemptions, in the Government's view, must therefore be on a basis of need. Accordingly people drawing National Assistance benefit and war pensioners had been exempted. Where there was hardship beyond these two groups the National Assistance Board was empowered to help.

Turning to the charges for appliances, Miss Hornsby-Smith pointed out that these would be limited to four items: surgical boots, surgical belts, wigs, and elastic stockings. No charge would be made for appliances for children under 16.

She defended the dental charges on the ground that this was the place in the service where savings could best be made. The patients were generally active and in regular employment: and it was hoped that these charges would increase the attention given to the priority classes of children, adolescents, and expectant mothers. To lessen the effects of the charges where there seemed special reason the priority classes had been exempted, and for adolescents the age of exemption extended to 21. It had also been decided not to charge for the initial examination and report. In conclusion she challenged the Opposition to say, if they persisted in repudiating these charges, how they would make up the deficit on the Estimates. Or were they prepared to allow the expenditure on the health service to rise without limit?

Mr. H. A. MARQUAND welcomed the modifications made in the Bill, but said that it remained thoroughly objectionable in principle. In his view it was unnecessary to have made such generous gifts to those who paid income-tax and to make savings of this kind at the expense of the sick, of chronic sufferers, and of the disabled and afflicted. The Labour Party had introduced charges in 1951 during the period of rearmament, but they were not intended to be permanent and a time-limit was set to them. If the Labour Party were returned to power, Mr. Marquand continued, "we shall take steps as soon as Parliamentary opportunity permits, to bring all these charges . . . to an end."

The third reading was carried by 284 votes to 266.

Dangers of Toxic Substances in Agriculture

In the House of Lords on April 29, Lord CARRINGTON, joint parliamentary secretary to the Ministry of Agriculture, moved the second reading of the Agriculture (Poisonous Substances) Bill, which he said had become necessary because of the increasing use in agriculture of poisonous substances as insecticides and weed-killers. The Government believed that enough was now known to justify regulations. The regulations, for which this Bill accordingly provided, would follow the lines of the recommendations put forward last year by the Zuckerman working party, which include the provision of protective clothing. The Government had at present no power of enforcement of the precautionary measures, and it was apparent that voluntary precautions were not enough. There was general agreement that precautions should have statutory backing and that definite obligations should be placed on both employer and employed.

For some matters, for the time being at any rate, voluntary arrangements would continue, either because enough experience had not yet been gained, or because there was insufficient agreement. Medical examination, for example, was one. But regulations would be made at once to deal with protective clothing, washing facilities, cleanliness generally so as to avoid contamination, periods of work, supervision and training of workers, the keeping of records, and the notification of sickness and accidents. In the first instance the Bill would apply to two classes of substances—dinitro compounds, such as dinitro-*ortho*-cresol (D.N.O.C.), used for spraying as weed-killers; and organo-phosphorus compounds, used as insecticides. The Minister would have power to extend the scope of the Bill to other substances by order.

Lord DOUGLAS OF BARLOCH regretted that the Bill did not protect the public generally. Some of these poisonous substances, he said, were used in the form of sprays and it was easy for small drops to be carried three or four miles on a breeze. It had already happened that innocent passers-by had been poisoned. The Zuckerman report had drawn attention to this. There was also the wider problem of the effect of these substances on the people who consumed agricultural products. It had been found by experiments upon test animals that D.D.T., and a number of substances of that chemical group, produced liver injuries.

Lord CARRINGTON, replying to the debate, said the recommendation of the Zuckerman working party that the words "deadly poison" should be put on containers had been referred to the Poisons Board. The board was rather against such a step, because they felt it would detract from the use of the word "poison" without qualification on other poisons which were sold in shops. However, the board recommended that manufacturers might apply the word "poison" followed by these words:

> "Caution. This substance is poisonous; the inhalation of its vapour, mist, spray or dust may have harmful consequences. It may be dangerous to let it come into contact with the skin or clothing."

The working party were inquiring into the effect of these poisons on the consumer, but there was no evidence to show how they could have any such effect. Certainly in this country there was no evidence that D.D.T. had been harmful to human beings. He thought that noble Lords had been unnecessarily anxious about the danger of spraying these substances. These poisons were cumulative and it took a comparatively long time to get any kind of dangerous dose from these sprays. The Bill was read a second time.

QUESTION TIME

Recruitment of Nurses

Mr. R. W. SORENSEN asked the Minister of Health how far the supply of trained nurses and probationers in hospitals had improved during the past 12 months; and approximately the ratio of patients to nurses in the main London teaching hospitals compared with other hospitals in the London area.—Mr. H. F. C. CROOKSHANK replied: During the twelve months ended Dec. 31 last the number of trained nurses and midwives in hospitals in England and Wales increased by 1873 full-time and 441 part-time, and the number of student nurses by 520. The ratios of patients to nursing and midwifery staff in hospitals in the Metropolitan area were 1·24 to 1 in teaching hospitals, and 2·89 to 1 in other hospitals.

Difficulties of British Hospital in Paris

Mr. H. F. L. TURNER asked the Secretary of State for Foreign Affairs if he would prevent the closing of the British Hertford Hospital in Paris.

Mr. H. A. NUTTING replied: No decision has yet been taken by the management committee to close the hospital. Offers of support have been received from the French ministry of health, and a subcommittee has been appointed to examine proposals for the general reorganisation of the hospital. Owing to the steep rise in the cost of living in France, the endowments which before the war met about half the annual operating-costs of the hospital, now barely cover expenses for one month. Though every effort has been made to meet the deficiency by local subscriptions and other means, the hospital committee has decided that the institution cannot be continued as it has been in the past. I am informed that most British residents in France are eligible for medical assistance from the French authorities.

National Insurance Sickness Benefits

In answer to a question Mr. OSBERT PEAKE, Minister of National Insurance, stated that about a quarter of a million people drew sickness benefit for a full year in 1950.

Immunisation against Foot-and-mouth Disease

In answer to questions Sir THOMAS DUGDALE, Minister of Agriculture, stated that the principal drawbacks of a policy of immunising animals against foot-and-mouth disease were that no known vaccine protected against all the types of the virus to which our livestock were exposed, and that the protection against particular types was of relatively short duration. It would, therefore, be impracticable to keep all, or even most, of the susceptible animals in this country in a satisfactory state of immunity. On the other hand, the immunisation of animals after an outbreak had occurred was not effective in preventing the spread of disease, because it took two or three weeks after inoculation before immunity was produced. Moreover, the presence of immunised animals among our livestock would tend to perpetuate the disease, since an immunised animal might become infected and while showing little or no sign of illness might infect other animals. Consequently, an immunisation policy would lead to foot-and-mouth disease becoming established in this country and was incompatible with the policy of stamping out infection by slaughter, which, he was satisfied, was the cheapest and most effective in the circumstances of this country and which had the support of the leaders of the agricultural industry. Research into foot-and-mouth disease, including the use of vaccines, was given the fullest backing through the Agricultural Research Council and through the Ministry of Agriculture.

Reciprocal Social Services Agreements

Sir IAN FRASER asked the Minister of National Insurance what negotiations had taken place with foreign, Commonwealth, and Colonial governments in the matter of old-age pensions, free or assisted medical services, and similar benefits.—Mr. PEAKE replied: A reciprocal agreement covering contributory old-age pensions and certain other cash benefits has been concluded with France and a similar agreement with Italy is awaiting ratification. Agreements on unemployment, sickness, and maternity benefits have been reached with the Irish Republic, and an agreement on family allowances with New Zealand. A multilateral agreement providing for medical care for persons without sufficient resources has been concluded between the Brussels Treaty countries, and another is being negotiated in the Council of Europe. Negotiations for bilateral agreements on various social-security benefits are taking place with the Netherlands, Belgium, Luxembourg, and the Federal Republic of Germany, and on old-age pensions with Australia and New Zealand.

War Department's Pay to Civilian Doctors

Replying to a question, Mr. ANTHONY HEAD, Secretary of State for War, said that the rate of pay of civilian medical practitioners employed on a full-time basis by the War Department was £3 10s. a day.

In England Now

A Running Commentary by Peripatetic Correspondents

FOR two spring days at Oxford the Society for General Microbiology sat on the hard seats of the theatre which saw the debate between Bishop (Soapy Sam) Wilberforce and T. H. Huxley ("I would rather be descended from an ape than from a divine who employs authority to stifle truth"). The society, discussing the multiplication of viruses, was no less in earnest but more mannerly than those who talked of the descent of man, and there was general agreement that a renewed session some years hence will be attractive and profitable. Technical skill will have provided stronger spectacles; some words said last month will have to be forgotten; there will be new faces but, let us hope, all the old ones. The only pity was that so few among the audience were doctors, who see viruses wild in the jungles of the body. But, all in all, it was a great occasion; and the visitors saw Oxford in April loveliness:

> "With its fair and floral air
> And the love that lingers there
> And the streets where the great men go."

* * *

I wish someone in the summer exhibition of the Royal Academy had painted this year's Boat Race. None of the wintry scenes I saw there came up to that strange flurry of snow, the thin streaks of racing boats, the rush of launches, and the little black figures prancing on the distant white bank. Still, there was one snow picture which took me pleasantly aback—Julian Trevelyan's "Winter Scene," where a fox in one half of a snowy wood matches a fox-coloured child in the other half. On the whole, though, there was less snow about than usual, thanks to the mild winter. Light effects had to be achieved in other ways, and Dame Laura Knight, in particular, has succeeded in painting the impossible in her "September Evening." Here the late sun is stabbing sharply through a clump of trees, straight into the eyeball. When that happens we do not look at the sun: it is too painful. Here, too, there is nothing to be gained by looking directly at the heart of the picture, which shows merely a white disc set in a sprawl of orange, like a reversed poached egg. But move the eye ever so little to the periphery, so that the image of the disc falls not on the macula but on the outlying retina, and the sun lights up like a torch. It is an artist's trick, but a strange one, which captures that common evening experience, and partly analyses it. It reminds us how puzzling is this convention by which scenes are usually painted with every part in focus, whereas in fact we see a tiny sharply focused area surrounded by a mere impression of distorted shapes and colour values; and some of the values seen at the periphery are brighter than those perceived by the macula. Otherwise Dame Laura takes us mainly among her favourite backstage and circus company; and so does Stephen Spurrier in his "Juggler Practising" and "Dressing Room." But people of this kind tumble too readily into pictures, and I was glad of a change of scene in "The Party," where he uses the same pale easy colours to show the well-stuffed children and the tired adults round a loaded tea-table.

Tough scenes were scarce, but Eric Kennington has gone back a couple of wars to show us "The Kensingtons at Laventie," arresting because of its clever pattern, but incurably romantic. William Roberts, also harking back, gives a surprising version of "The Revolt in the Desert," where Lawrence and his Arab chieftains appear in a solid clump reminiscent of the pictures in appliqué work produced so freely in that part of the world. The limitations imposed by his materials on an Arab boy set down to a bit of hemming do not affect the painter in oils, however; and it seems rather masochistic of Mr. Roberts to trammel one art with the restrictions of another.

There are some good medical portraits—particularly those of Lord Webb-Johnson and Dr. Charles Hill, by T. C. Dugdale. I confess to being momentarily astonished by the appearance of Dr. Hill, having misread my catalogue and expected a bowl of fruit. Pietro

Annigoni's portrait of Lord Moran has already been admired in medical circles and stands up well to further study. David Jagger's painting of Dr. W. S. Fox is just the thing for a clinician, every detail being beautifully and carefully observed and represented, with respect for texture, surface, colour, and volume. Had Dr. Fox presented, on inspection, the smallest clinical sign we can feel sure it would have been faithfully reproduced. As it is he can look himself over and pass himself A1. A much vaguer, but none the less agreeable, portrait by Clive Gardiner shows "P. D. Trevor-Roper, Esq., F.R.C.S.": and of course there is Sir Alexander Fleming, this time by Henry Holt. Henry Lamb, our medical representative among the artists, has done several nice portraits, including one of Prof. T. F. Hewer. I liked his street boys in "Sketch for Night Life," and his "Men of Auzay" playing cards.

I also remember with pleasure the washed-out reds of Derek Lawrence's "Fishermen of Kyrenia, Cyprus," the grey and gold plumage of C. F. Tunnicliffe's "Barn Owl," and the soft weather in R. Vivian Pitchforth's "North Wales Coast." Hayward Veal's "Academician Resting" confirms my belief that academicians rest by retiring into a fog.

* * *

SIR,—Your correspondent's idea of bringing up babies in the posture they are used to is not original. My parents put the idea into practice years ago. In fact I am having my turning-up party next month.

B.T.M. Upp.

* * *

The appearance of a new racquets champion is a rare event; but when G. W. T. Atkins won the Amateur Racquets Championship at Queen's only a hundred or two spectators saw him do it. His predecessor, D. S. Milford, is now 46, so one can readily believe the newspaper comment that he was less fleet of foot than last year, when he won the championship for the seventh time in 20 years. Youth must constantly be usurping middle age and no-one cares how the older generation fares. Orators go on improving their speaking indefinitely, and a master of phrases will still produce new ones, like "The Soul of Honesty," at any age, but in most games a man over forty stands little chance against opponents in their twenties. Experience counts for something to offset differences in age, even in a fast game like racquets, as Atkins (aged 25) showed when he beat M. C. Cowdrey (aged 19); but Atkins won because of the perfect timing of his strokes and the magnificent coördination between all parts of his body exemplified by his fine footwork.

Driving along Western Avenue to the match I passed two aged cars, old crocks that first took the road about the turn of the century but were keeping up a steady 30 m.p.h. They had lasted so long because they had been kept in good order; and they carry a lesson for all athletes—indeed, for all of us. If we cared for our bodies as these cars had been cared for fewer of us would be told after middle age that our hearts were feeling the strain. I had read in a paper that day how 60% of the 200 doctors at Mount Sinai Hospital had symptoms referred to their hearts, and yet most of them would not reduce their weight though they gave this advice to their patients.

Returning to the racquets championship: How long will the new champion last? Will Milford come back once again, or, more likely, will the boy of 19 revenge his defeat when he is 20? In any case, Milford has set us all an example, for even if at 46 he is now too old, at 42, 43, 44, and 45 he could beat all comers.

* * *

News from School.—"Re the pigeon I brought back: I got a biscuit tin (half cube) and wrapped the plucked and paunched pigeon in well-buttered greaseproof paper. An electric fire in a study was placed on its back and the tin placed on the fire for 40 minutes approx. The smoke went up the chimney, and at the end of the above mentioned time the pigeon was well roasted, and made excellent eating. Last night we had prep instead of an entertainment, but I was quite glad because I had an essay on sewage-disposal to complete. I have bought a bow-tie. It is a ready-made clip-on one. Unfortunately bow-ties are illegal except in our own time. The tie is blue, red, yellow, and green, and looks jolly good."

Letters to the Editor

RELAXATION IN LABOUR

SIR,—From your review (April 19) of *The Queen Charlotte's Textbook of Obstetrics* readers might assume that "relaxation" is unknown at Queen Charlotte's Hospital. On the contrary the hospital has a large department organised by one of the pioneers of antenatal physiotherapy—an enthusiastic worker who has the advantage of being a midwife as well as a physiotherapist.

Yet your reviewer's implication that "relaxation" is now generally accepted as an essential part of obstetric practice should not pass without comment. In the first place "relaxation" is not a form of treatment which can easily be prescribed by all and sundry. Badly done, it is worse than useless—we have now gone so far that a woman who complains of pain in labour may be accused of "not relaxing." In the second place, what evidence (with proper controls) has been produced to show that antenatal physiotherapy reduces the incidence of inertia, delay in the second stage, or perineal damage? All will agree that when a patient is placid in labour her confidence ensures her coöperation, and her lack of fear diminishes the distress due to pain. Yet are we to believe that this self-confidence can only be given to her by some particular form of exercises and relaxation? How, for instance, can "relaxation" affect uterine contractions and the pain of cervical dilatation except through the mind? It may be found that equal mental effects can be secured by other means. Anyone who has had the personal care of patients in labour knows how well the fearless and happy get on—without any system of "relaxation."

Anything which combats fear in labour is valuable, including antenatal physiotherapy, but let us not pretend that this is some new physiological discovery, or that any woman can secure an easy labour if only she will follow some ritual.

Although I have expressed my personal opinions, they are shared in part or in whole by several of my colleagues, and the omission of "relaxation" from this textbook may be explained—at least until more evidence is available. We are planning an investigation which may allow us to weigh this evidence.

Queen Charlotte's Hospital,
London, W.6.
S. G. CLAYTON.

CŒLIAC DISEASE

SIR,—The article by Dr. Anderson and her colleagues in your issue of April 26 would appear to throw a light on a much wider problem of medicine—that of "fat intolerance." For some years there has seemed to us to be a clinical association between cœliac disease and the condition generally known as "ketosis" in childhood. Work by one of us on 400 school-children in the L.C.C. nutrition centres, with a follow-up of five years in some cases, and observation of cases seen by both of us in the child-guidance clinic at Bromley over the last seven years, has produced evidence which supports this view, especially in the light of the paper by Dr. Anderson and her associates.

In the series of 400 children, one of us showed the association between a number of clinical manifestations and "ketosis."[1]

The "ketotic" child commonly shared with the cœliac child certain physical characteristics—namely, a large blown-out abdomen, and a hip measurement substantially less than the mean chest measurement and sometimes less than the completely expired chest. These characteristics were proportional to the severity of the "ketosis." The average child has a hip measurement that is equal to, or greater than, the expanded chest.

After convalescence with a controlled diet most of these children showed an increase in the hip measurement and a decrease in the abdomen measurement: they differed in this way from the average child, with the exception of those who were frankly undernourished, which suggested to us that these anomalies in body measurement in "ketotic" children are a function of malnutrition due to defective absorption.

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[1] Morgan, G. D. *J. ment. Sci.* 1949, 95, 401.

Before the late war these children were treated by a substantial reduction in their white bread and carbohydrate intake generally, with an almost total elimination of milk from their diet, and the addition of glucose, 'Marmite,' and fruit and salads. During the war the shortage of protein foods made the deletion of milk dangerous. Nevertheless it was found that the all-round reduction of fats and starches, with the addition of marmite in large quantities, apparently increased the tolerance of these children for milk. During the last seven years we have limited the intake of fats and carbohydrates and added large doses of vitamin-B complex. As a result of this, even whole milk appears to be easily tolerated. Vitamin-B complex has been used to avoid the risk of precipitating other manifestations of vitamin-B deficiency, in preference to nicotinamide, which we have found equally efficient.

Both mothers and children notice a difference when the child has adhered to the diet for as little as a fortnight; and both are far more enthusiastic about vitamin-B-complex supplements than either vitamin C or vitamins A and D, which were tried by themselves at different times before the publication of the American work on nicotinamide in the early 1940s.

The psychological make-up of the "ketotic" child, whose precocity, sulks, and tempers are similar to those of the cœliac child, becomes normal on the diet, but tends to relapse after a stay with a mistakenly indulgent relative. Chilblains, occurring in 15·5% of "ketotic" children, totally disappeared on this régime. The incidence of chest deformities, of the type usually regarded as rachitic, was 38% in "ketotic" children, compared with 13% in the rest of the children in the group.[1] Headaches, abdominal pain, and diarrhœa showed a similar association with "ketosis."

The severity of chest deformity appeared to be in direct proportion to: (1) the child's "ketosis," (2) his physical build, and (3) poverty. Careful investigation, particularly investigation of different members of the same family, enabled us to assess clinically whether the first two or the third factor was operating more severely in the individual case.

Before the late war, and now again in the lower-income levels, the working-class diet for children consists excessively of bread and margarine (fortunately mitigated by the addition of school milk and school dinners)—a diet which is likely to magnify the severity of the condition. In the child in the higher-income levels before the war there was a tendency, both on the part of mothers and of their dietetic advisers, to overload the diet with heavily refined starches and milk fats. Correction of these factors, in our experience, will transform the temperament of many children whose history suggests "ketosis," and who look pale, puffy, and unhappy when they first attend the child-guidance clinic.

Observations on the temperamental characteristics of "ketotic" children, and their response to particular dietary corrections, had already led us to the conclusion that "ketosis" could be regarded as a mild manifestation of a condition of which the fulminating form is cœliac disease; in the latter the onset is earlier, and the severity is such that the child is fighting a losing battle. In both conditions a genetic factor (probably the same factor) is important, and may be responsible for other metabolic and endocrinological upsets—hence the relationship between "ketosis" and chest deformities, and also "ketosis" and physical type. The determining factor, however, would appear to be dietetic, although it must be recognised that there is a relationship between the strength with which the genetic factors operate and the level of dietetic indiscretion necessary to evoke the manifestations. In one family both "ketosis" and cœliac disease appeared in different members, and the severity of "ketosis" and the build of the child ha invariably been related.

Sheldon in Wolverhampton observed that a fairly lar group of elderly persons gave a history of life-lo aversion to fat. His observation has been confirmed our elderly patients. We have also seen a number patients in the intermediate age-groups who ha histories of vomiting or nervous diarrhœa in adult li following a history suggestive of "ketosis" in childhoo In both groups there is a dramatic improvement general health on reducing the intake of white flo products and fat, and administering nicotinamid We believe that these groups are examples in later adu life of the same syndrome.

G. D. MORGAN
London, W.2. ELIZABETH TYLDEN.

COÖPERATION IN CARE OF THE TUBERCULOUS

SIR,—The public-health section in your issue of April 2 contains two notes which bring out forcibly the no sensical attitude which would appear to be permeatin central administrative departments in relationship t tuberculosis. The first note tells of the revised reg lations for the notification of tuberculosis, which make i no longer compulsory for a medical officer of health t keep a tuberculosis register or for sanatoria or hospita to keep the medical officer of health informed of patien admitted or discharged.

The second note concerns a Ministry of Health circula letter, based upon the present lack of coöperation betwe hospitals and public-health departments, which as sanatoria and hospitals to notify medical officers health when cases of tuberculosis are admitted or di charged. This circular also states "that not all che physicians are sufficiently concerning themselves in th preventive and aftercare aspects of tuberculosis work.

Although all this refers to England and Wales, on feels compelled to draw attention to what appears t be a contradiction in outlook in central administrati circles. How on this earth can a medical officer of healt efficiently carry out his duties in connection with tubercu losis if patients wander in and out of hospitals onl notified at the whim of hospital authorities? The mos recent regulations accentuate the unbelievable confusio in the management of this unfortunate disease.

Public Health Department,
Dingwall, Ross-shire. J. LANDESS HORNE.

MEDICAL ASPECTS OF THE KOREAN CAMPAIG

SIR,—Your annotation of April 12 mentions th "acute epidemic hæmorrhagic fever" encountered i Korea and I would like to add some further detail

At least seven different virus infections are endemi at various places in the Soviet Union which produc the same clinical symptoms, with petechiæ in the skin and other focal signs of a hæmorrhagic disorder, possibl of vascular and/or vasoneural origin.

These fevers were recognised and studied by Russia virologists—e.g., in Uzbekistan (1927), in the Far East of Siberia (1934), in Tashkent (1941), in the Crime (1944), in the Omsk district (1944), in Turkmenista (1946), and in Bukovina (1947). The virus is different in each area; its pathogenicity to man and animals the hosts and vectors of the virus, and the organs whic it attacks most severely all vary from place to place.

There are also confusing differences in the name given to the infections. While all of them might b called "endemic (or epidemic) hæmorrhagic fever," the Far-Eastern type has been referred to sinc its recognition as "endemic hæmorrhagic nephrosonephritis." Under this name it was buried as a strang local disease of the kidney of no general importance, forgotten or unknown in the Western medical world.

Last year I came across this term in the original Russian reports, which I had consulted to see whether they contained any descriptions corresponding to Japanese accounts of the hæmorrhagic diseases of Manchuria and Korea. I came to the conclusion that this kidney disease of the Russians was identical with the "epidemic hæmorrhagic fever" which the Japanese had recognised and described during their occupation of Manchuria, and which United Nations troops had encountered in Korea. My report[1] drew attention to the real nature and military importance of the disease.

It is a true virus infection, endemic in the cockpit of Asia, and occurring sporadically throughout the year with peaks in the spring and autumn. It is found on both sides of the Lower Amur River. The average mortality is 5%, but varies with the clinical type of the disease—i.e., grippo-typhoid, gastro-intestinal, uræmic, or meningo-encephalitic. The first type runs the mildest course and lasts about 3 weeks.[2]

As well as the mite, *Lælaps jettmari* Vitzthum, and the mouse, *Apodemus agrarius*, mentioned in your annotation, the Eastern vole (*Microtus michnoi pellicus*) is also a reservoir of the virus, and other parasitic arthropods are suspect.

Inoculation of virus-containing material reproduced the disease in monkeys and in 46 volunteers.[3-5] Intranasal intragastric, or intrapharyngeal inoculation of the virus by instillation, tamponade, or smear produced no reaction in the human body.

The failure of antibiotics means that the possibilities of specific preventive vaccines and of serum therapy need further study.

Washington, D.C. CLAUDIUS F. MAYER.

VARICOSE ULCERS

SIR,—Dr. Anning (April 26) states that "Superficial varicose veins, unaccompanied by dilatation of the deep veins, do not cause failure of the leg-muscle pump and are never responsible for ulceration." If I understand Dr. Anning correctly, the vast majority of cases of leg ulcer really have an associated insufficiency of the deep veins, and the rest have conditions of doubtful causation or arterial or arthritic disorders.

I agree wholeheartedly with his view that the wholesale treatment of leg ulcers by an assault on such varicose veins as present their blue and suffering backs to the injector's searing harpoon or the surgeon's knife is wrong in principle and disastrous in practice. There is nevertheless a definite group in which no visible trace of deep insufficiency can be found save only the disputed ulcer and its surrounding skin changes, but in which gross varicosities which fill from above seem to cry out for surgery, and in which a carefully planned operation is rewarded by rapid healing of the ulcer, disappearance of itching and other skin changes, and return to normal function.

Whatever the underlying pathology of this mysterious condition, the highly satisfactory results achieved by treating the superficial veins seems to suggest the existence of a true varicose ulcer.

York. J. K. WILLSON-PEPPER.

SIR,—The correspondence about the proper treatment of varicose ulcer is a good example of a phenomenon which is well marked in our profession—that is, the great difficulty in the spread of knowledge.

I am sure that there is no doubt that, as Dr. Rivlin and Dr. Anning say (April 26), varicose ulcers will rapidly heal if the œdema is prevented by wearing an efficient elastic bandage. Nevertheless up and down the country there are people who are patiently lying in bed waiting for their ulcers to heal or are having their superficial varicosities tied off or blocked up.

Now if I take my car to a garage with a broken cross-member, there is no dispute from garage to garage as to what is the best treatment. Once an efficient solution to the engineering problem has been devised its use rapidly becomes generalised. In medicine, however, there are numerous examples of controversy or ignorance about matters which should have been settled long ago—for instance, the so-called dangers of mercurial diuretics in congestive heart-failure; the giving of routine preoperative enemata, often fortified by soap or turpentine; putting bolsters under people's knees when they are confined to bed; and making the victims of peritonitis sit up in bed in the hope that pus will gravitate into the pelvis (the frequency of subphrenic abscess does not yet seem to have produced a pause for thought).

There are many examples of strange practices or ignorance of the success of established methods in medicine. I find this difficult to understand; perhaps our psychiatric colleagues can provide the explanation.

Plymouth. B. KENDRICK.

CAT-SCRATCH FEVER

SIR,—We read with interest your annotation of Feb. 9, in which you called on registrars to describe cases of cat-scratch fever in Britain. We describe here the first case *in* a registrar, one of us (E. S. K. C.) being the victim.

In November, 1951, the doctors' mess acquired a kitten, from which the patient subsequently received many superficial scratches on the hands. A raised erythematous plaque 8 mm. in diameter was first noticed medial to the nail of the fifth left finger at the beginning of January this year. Two weeks later there was discomfort in the left epitrochlear region, and by the next week the epitrochlear gland was enlarged.

The patient presented herself for examination on Jan. 31, when the left epitrochlear gland measured 10 × 6 cm., and two left axillary glands were 3·5 cm. in diameter; periadenitis was severe. Healing superficial scratches, which had never suppurated, were present on both hands, and the lesion on the fifth left finger was scarcely discernible. There was mild systemic upset, but no fever. The spleen was not palpable. No other abnormal physical signs were detected. Radiographic examination of the chest showed no enlarged hilar glands.

The patient was admitted to the ward. Procaine penicillin 300,000 units twice daily was given for seven days without effect. On the third day the digital lesion became a little inflamed, and a drop of serous fluid was exuded: the lesion subsided by the following week.

On Feb. 11 a ten-day course of aureomycin 500 mg. six-hourly was started. On Feb. 14 a left supraclavicular gland was found to be enlarged. By this time the periadenitis was much relieved, and the axillary glands were smaller; but the epitrochlear gland remained the same size. On Feb. 16 the patient went away for two weeks' holiday.

On Feb. 29 the swelling of the axillary and clavicular glands had subsided. The epitrochlear gland became fluctuant, and, on March 4, 4 ml. of yellowish pus was aspirated. Pus was aspirated on three further occasions, and the swelling diminished. By April 8 the gland was 2·5 cm. in diameter and, a sinus having formed, discharged spontaneously.

Investigations.—Hæmoglobin, red-cell count, total and differential white-cell counts normal. Frei test (March 4) negative. Complement-fixation test for psittacosis/lymphogranuloma-venereum (March 4) negative $< 1/10$.

Pus showed many degenerated polymorphs. No organisms were found by direct examination and culture; guineapig inoculation was negative. Antigen was prepared from the pus according to the method of Hanger and Rose, and 0·1 ml. injected intradermally; the reaction was strongly positive. Pus and serum were sent to the Virus Reference Laboratory, Colindale. No virus was isolated. but further investigations are being undertaken.

Now that attention has been drawn to the condition, many more cases will probably be reported. When the

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1. Mayer, C. F. Epidemic Hæmorrhagic Fever. 1951. Surgeon-General's Office, Washington, D.C.
2. Mayer, C. F. *Milit. Surg.* 1952, 110, 276.
3. Mayer, C. F. *Lab. Invest.* 1952 (in the press).
4. Kitano, M. *Nippon densenbyó gakkai zassi.* 1944, 18, 1.
5. Smorodincev, A. A., et al. Etiologia i klinika hemorragicheskaia nefrozo-nefrita. Moscow, 1944.

present victim was actually an inpatient we were having difficulty in making a diagnosis, but on reading the current *Lancet* found the solution. The kitten has remained in good health throughout.

We wish to record our thanks to Dr. L. Hewlitt, pathologist to Lambeth Hospital, for his interest in this case and his great help in carrying out the pathological examinations.

Lambeth Hospital,
London.

ELSPETH S. K. CAMPBELL
C. E. W. WHEATON.

CROSS-INFECTION IN THE WARDS

SIR,—I have long maintained that if the English climate were harsher we would have houses both warmer in winter and cooler in summer than those we now suffer.

Mrs. Geary's letter last week reminds me of the summers I spent in Toronto, where the day temperature seldom fell below 70°F, and where all windows and doors were screened against flies; these screens did nothing to prevent air circulating through the houses.

I am also reminded of the first night of my midwifery training, at a maternity hospital close to a tidal river. The night was hot, and while we waited in the labour ward for a patient to come into the second stage of labour we amused ourselves by killing the insects that had gate-crashed on our little party.

Of course, both Mrs. Geary's and my experiences show more how infection may be brought into a ward, than how it may be transferred from patient to patient once it is there. In this matter of insect control, however, it would be wise to consider the experience of those who live in an insect-ridden, continental climate.

London, N.W.3.

ROY MOTTRAM.

MEDICAL TREATMENT ABROAD

SIR,—The increased shortage of foreign currency owing to the prevailing economic difficulties has compelled the Treasury to ask their Exchange Control Medical Advisory Committee to reconsider the policy under which currency certificates are granted to patients seeking treatment abroad.

Until recently, currency was made available for treatment in countries of the European Payments Union in all cases of real illness, whether or not comparable treatment could be obtained at home or within the sterling area. It has now, however, become necessary to adopt a stricter policy and in future the normal rule will be to allow currency certificates only where the required treatment cannot be had in this country or elsewhere in the sterling area. The committee will pay regard to the length of journeys in determining whether or not the sterling area offers practicable facilities. Patients suffering from tuberculosis will usually be allowed currency for treatment abroad, and, during the winter months only, short visits for convalescence after serious illness may be permitted, especially in patients over 65. The rule that a husband or wife is allowed currency to accompany a sick partner abroad, when either of them is over 60, will still apply, and currency may also be allowed for companions in other circumstances where the committee consider that it is essential for them to go with the patient.

Under the new procedure the number of applications approved by the committee is likely to be smaller, but they are satisfied that under the revised arrangements it will still be possible for any person who is seriously ill to obtain any foreign treatment which is essential to recovery.

The committee's procedure is simple and elastic. The patient's doctor sends the application, with particulars of the case, direct to the Secretary, Exchange Control Medical Advisory Committee, Tavistock House North, Tavistock Square, London, W.C.1, and each application is considered individually upon its own merits. The committee, which is composed of medical consultants, bases its recommendations, within the above general limits, solely upon medical grounds.

The members of the committee continue to be grateful to the medical profession for their support in this difficult task. Doctors are most helpful in presenting only suitable cases, and when, unfortunately, applications have to be declined, the committee fully realise that the hard task of explaining the situation to the patient generally falls upon the doctor.

HARLEY WILLIAMS
Secretary.

EFFECT OF A.C.T.H. ON HOMOGRAFT SURVIVAL

SIR,—We were interested to read that Dr. Butterfield and his colleagues (April 12) think that A.C.T.H. treatment may have prolonged the life of homografts in 2 out of the 3 patients that they treated. There are, however, two statements in their paper that need some correction:

1. We are reported as having had "negative results" with cortisone in animals. On the contrary, we feel that a threefold or fourfold prolongation of the life of homografts in rabbits[1] constitutes a very definitely positive result unless permanent survival is to be the only criterion of success. Morgan,[2] also working on rabbits, and Cannon and Longmire,[3] working on chicks, have had similar results.

2. Dr. Butterfield and his associates, presumably referring to A.C.T.H. activity, suggest that duration of the survival of homografts may be related to the intensity of the adrenocortical activity in the host. "A similar relation," they say, "between duration of survival and the dose of 'Cortone' in rabbits has been noted by Sparrow (1951)." We have no reason to disbelieve this statement, but it is not what we have noted. Miss Sparrow's work, as yet unpublished, has been carried out [illegible] shown that—on a weight-for-weight [illegible] quires much larger doses of cortisone [illegible] to achieve a comparable effect. No attempt has been made to assay cortisone activity in terms of its ability to maintain homografts.

University of Birmingham.
University College, London.

R. E. BILLINGHAM
P. L. KROHN:
P. B. MEDAWAR.

SAVINGS ON THE N.H.S. DRUG BILL

SIR,—It is not a little surprising to find in the annotation under this heading (March 22) a statement implying that bismuth carbonate, the glycerophosphates, and creosote are useless remedies.

Surely the older, and therefore much more experienced, physician knows the great value of creosote in medical practice. Personally I have for years prescribed creosote in laryngeal and bronchial affections with very great benefit. As for bismuth carbonate, I am well aware that the modern practitioner regards it as an inert drug, but that is very far from being the case. Some of our most highly qualified practitioners speak of it in terms of the highest praise. I have used it with excellent results, not only in simple gastric ailments but also in cases of peptic ulcer. I am convinced that if this condition were diagnosed in the early stages and bismuth carbonate prescribed in appropriate doses, no operation would be necessary.

I am afraid that today the older and well-tried as well as safe remedies are being too often discarded in favour of the newer and often dangerous ones. One of the best examples of this is the barbiturates. By all means let us not regard the older and safer drugs as out of date, but rather continue to prescribe them more frequently than we do at present.

Edinburgh.

JAMES BURNET.

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1. Billingham, R. E., Krohn, P. L., Medawar, P. B. *Brit. med. J.* 1951, i, 1157.
2. Morgan, J. A. *Surgery*, 1951, 30, 506.
3. Cannon, J. A., Longmire, W. P. jun. *Ann. Surg.* 1952, 135, 60.

POSSIBLE DANGER WITH CYCLOPROPANE

SIR,—In his letter of April 26 Dr. Russell suggested that a separate screw-valve be fitted on the cyclopropane rotometer. This was originally standard on machines, but in the light of experience has been abolished. The disadvantages, I believe, were bursting or blowing off of the tube or connections owing to a gradual build-up of pressure when the screw-valve was off and the main valve left on; and also the action of the cyclopropane under pressure caused chemical changes in the tubing with weakening and formation of a dust which got blown into the rotometer causing inaccuracies and sticking.

I agree with Dr. Russell's main contention that there is room for improvement in the present method of control; perhaps with a better-designed coupling, and tubing made of one of the modern plastics which remains inert in the presence of cyclopropane under pressure, we could return to screw-valve rotometer control.

London, S.W.1. G. F. PANTON.

SIR,—Dr. Russell's letter brings back to my mind two similar experiences.

A child was undergoing tonsillectomy. The anæsthetic was oxygen over ether on a Boyle Davis gag. I suddenly realised that the rhythm of the child's respiration had changed: the breathing was shallow and quiet. As the operating-theatre was blacked out, it had escaped my attention that a nurse had brushed by the cyclopropane key and had turned it full on.

The second case was even more dramatic.

A healthy young man was undergoing meniscectomy. The anæsthetic was thiopentone, pethidine, and gas and oxygen. I suddenly realised that the patient had stopped breathing. While turning off the nitrous oxide, I saw the cyclopropane bobbin full on.

Ever since, I have made it a rule to have the cyclopropane key removed if cyclopropane is not to be used.

St. Olave's Hospital, London, S.E.16. H. H. WEISZ.

DOMICILIARY CONSULTATION IN PSYCHIATRIC PRACTICE

SIR,—It was both interesting and instructive to read Dr. Leigh's article last week.

I agree with most of Dr. Leigh's observations, basing my own views on a somewhat greater number of cases over a corresponding period. One finds in Manchester that it is not so much the fear of certification that restricts patients' visits to the psychiatrist, but rather the fear of the type of person the patient will meet either in a mental hospital or in the psychiatric wards of a general hospital. These wards are definitely of great benefit today, because many patients are willing to come into a general hospital whereas they would be averse to admission as voluntary patients to a mental hospital. However, the aversion to entering a local mental hospital depends very often on the *reputation* of that hospital, and there is no doubt that as the standards and freedom from overcrowding improve, so will the reputation of these hospitals be enhanced.

I entirely agree with Dr. Leigh that the domiciliary consultation in psychiatry is more suitably conducted in the absence of the general practitioner. I always prefer this unless the general practitioner particularly wishes to accompany me. Not only does it save the time otherwise spent in arranging a mutual appointment (which these days is often far from easy), but, as Dr. Leigh says, patients will tell the consultant many things which they have never admitted to their doctor for fear of disapproval.

The development of psychiatric wards in general hospitals has, with the development of physical and chemical methods of therapy, allowed patients to be admitted urgently and without certificate when perhaps there were no mental hospital beds in the area available at that time. The combined use of domiciliary consultations with these beds has certainly been in Manchester of inestimable value, especially in the treatment of the depressive states amounting sometimes even to stupor. The risk of suicide has to be accepted, but one can only base one's opinions on clinical judgment; and my figures of suicide agree with Dr. Leigh's. Every psychiatrist loses patients in this way at some time or other, however careful he may be.

I should have liked to have seen Dr. Leigh mention coöperation between the consultant psychiatrist and the duly authorised officer. In the past the relieving officer, like the municipal hospital, was often a servant of the public with little say of his own; but now the authorised officer with the mental health department of the local authority can do a great deal in differentiating the really acute from the not so acute case; and coöperation between the consultant, the general practitioner, the authorised officer, and the mental hospital in the area can, I believe, save much time, much expense, and much unhappiness. In the Manchester area we are blessed, I believe, with this coöperation.

Manchester. NORTHAGE J. DE V. MATHER.

SIR,—Dr. Leigh's article was most welcome. We feel sure that he does not stop short at the single visit, but would be prepared to continue visiting those patients and their relatives who are unable or unwilling to attend the outpatient department or enter hospital. The field here is considerable; but the visits, if paid in conjunction with the hospital's psychiatric social worker or with the staff of the local authority's mental health service, should not prove insuperably time-consuming. Dr. Leigh does touch briefly on the idea of developing a "district" psychiatry service, which might well include the junior medical staff.

We enjoyed, too, his remarks on the need for preliminary experience in general practice. No doubt, while working in the outpatient department Dr. Leigh has felt the need to see his patient at home, and to sense the emotional stresses in the family circle. We have many times telephoned the family doctor asking permission to visit, perhaps with the duly authorised officer, probation officer, or other social worker, and we have never known a refusal. Some doctors, indeed, have been good enough to invite one of us (J. C.) to sit with them during the evening surgery in order to estimate the size of the psychiatric problems in their practices.

Since 1949 the consultant staff of this hospital have made some 150 visits in direct response to a call from the general practitioner, besides many others asked for by the local authority's staff and the probation service. If possible the patient's own doctor attends, but now that relations have been established he is often content to allow us to go alone and to rely on the subsequent written report.

Our one criticism of Dr. Leigh's article is of his constant stress on the need to avoid certification. It was, for instance, a little difficult to picture his disturbed patient, struggling, shouting, and behaving impulsively in the outpatient department, yet being admitted to hospital as a voluntary patient. It may be that the doctor calls the mental-hospital consultant when he foresees the need for certification, for of our 150 patients slightly more than a fifth required certification before admission.

It is particularly in these cases that the domiciliary visit is so valuable. The second opinion can do much to resolve the doubts of the relatives and uphold the rightness of the family doctor's decision. For who is better qualified to write the certificate than the patient's own doctor, rather than some stranger who may be meeting him for the first time? One doctor has expressed the fear that by certifying he might lose the patient and the relatives and indeed the whole street, but this seems most unlikely. The opportunity can be taken to explain the modern working of the mental hospital and to dispel the common fear that the patient is "being put away for ever." The doctor, too, who does not often write a certificate may welcome some advice on the procedure.

The great majority of our certified patients were suffering from severe psychosis, but 5 were borderline and might at length have been persuaded to come in voluntarily. 3 were women past middle age suffering from depression with hysteria, and 2 were adolescent schizophrenics.

The decision to certify is indeed a hard one, but experience shows that this type of patient commonly insists on leaving hospital in the middle of treatment, after three or four weeks of doubt and vacillation. We have had much discussion on this subject, and consider that there is a place for regarding the certificate as a positive therapeutic measure, saving the patient many weeks of illness or even chronicity.

J. P. CHILD
J. COWEN
J. W. MACPHERSON.

St. Nicholas Hospital,
Newcastle upon Tyne.

LACTOSURIA FROM CUTANEOUS ABSORPTION

SIR,—In the exposure method for the treatment of burns it is common practice to apply penicillin-lactose powder to the raw areas. Recent studies on the urine of severely burned patients have shown the presence of reducing sugar several days after the initial glycosuria commonly found in severe trauma. Ward tests with Fehling and Benedict's solutions were strongly positive, but with phenylhydrazine lactosazone was formed. This had a melting-point of 200°C, and the identity of the sugar was further confirmed by isolation in the solid state and preparation of the octo-acetate with melting-point 96°C.

Chromatography by Partridge's[1] technique of serial specimens of urine from two severely burned patients (67% and 60% surface-area) has confirmed the initial true glycosuria of the first 24 hours. In our cases this was followed by a sugar-free period until about the fourth day, when lactose appeared in large quantities. At this time the patients were receiving lactose in two forms: in milk feeds and in local penicillin powder. Milk contains 4–5% lactose and might cause lactosuria if given in sufficient quantity to overload the lactase of the intestinal juice. Careful review of the clinical histories showed that lactosuria could appear before milk was started and disappear while milk was continued. On the other hand, the onset in both patients coincided exactly with commencement of the use of penicillin-lactose powder, and cessation immediately followed use of penicillin cream instead of the powder. Tests on other patients have shown that milk feeds up to 2 litres per day do not cause sufficient lactosuria to give reduction of Fehling's solution (0·3 ml. in 5 ml. mixed Fehling) though just detectable amounts of lactose can be found by chromatography of the urine.

We do not know of any harmful effect of this absorption and excretion of lactose, though the possibility of renal tubule damage, as has been attributed to sucrose,[2] should perhaps be borne in mind. These findings should, however, remind us of the great absorptive capacity of the large raw areas of burns and possibly other skin lesions; and, secondly, that reducing sugars appearing in the urine may have entered the body by this route.

S. BAAR
J. P. BULL.

M.R.C. Industrial Injuries and
Burns Research Unit,
Birmingham Accident Hospital.

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[1] Partridge, S. M., Westall, R. G. *Biochem. J.* 1948, 42, 238.
[2] Anderson, W. A. D., Bethea, W. R. *J. Amer. med. Ass.* 1940, 114, 1983.

Public Health

Sanitary Inspectors' Working Party

LAST year the Minister of Health set up a working party "to inquire into the nature of the work at present being done by sanitary inspectors and the nature and functioning of the present arrangements for their recruitment, training, and qualification, and to report on the adequacy of such arrangements." Persons or bodies who wish to submit evidence should write to the working party's secretary, Mr. W. A. Fuller, Ministry of Health, Savile Row, London, W.1.

Heat Treatment of Ice-cream

By the two methods hitherto approved in regulations for the heat treatment of ice-cream, the mixture is kept at a temperature of either (*a*) not less than 150°F for 30 minutes, or (*b*) not less than 160°F for 10 minutes. Under the Ice-cream (Heat Treatment, &c.) Amendment Regulations, 1952, which came into force on May 5, a third method is approved. By this method the mixture must be kept at a temperature of not less than 175°F for 15 seconds in thermostatically controlled apparatus.

Smallpox in South-east Lancashire

There has been no further notified case of variola minor in South-east Lancashire since April 17, and the medical officers of health of Rochdale and of the surrounding districts which were affected by the outbreak have reported that all known contacts are out of surveillance. A few patients are completing the necessary period of isolation at Ainsworth Smallpox Hospital. There are good grounds for believing that this outbreak is over.

Death-rates in 1951

The Registrar-General[1] reports provisionally that in 1951 the rate for maternal mortality (excluding abortion) in England and Wales was 0·65 per 1000 live and still births. This is the lowest rate yet recorded. The neonatal death-rate was 18·8 per 1000 related live births.

All forms of cancer accounted for 2115 deaths per 1,000,000 population in men and 1822 per 1,000,000 in women, compared with 2058 and 1840 in 1950. The rise in the rate for men includes an increase from 484 to 530 per 1,000,000 population for deaths from cancer of the lung and bronchus.

The provisional death-rate from respiratory tuberculosis was 275 per 1,000,000 population—a decrease of 14% from the previous year, in which the rate was 20% below that in 1949. The rate for other forms of tuberculosis was 41 per 1,000,000 population, compared with 43 in 1950.

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[1] Registrar-General's Return for the Week ended April 26, 1952. H.M. Stationery Office. Pp. 20. 1s.

Infectious Diseases in England and Wales

Disease	Week ended April			
	5	12	19	26*
Diphtheria	22	24	32	35
Dysentery	548	489	327	275
Encephalitis:				
Infective	1	1	6	2
Postinfectious	3	1	2	4
Food-poisoning	185	52	64	123
Measles, excluding rubella	6836	5176	6775	6137
Meningococcal infection	60	41	48	46
Ophthalmia neonatorum	38	32	44	49
Paratyphoid fever	7	13	9	8
Pneumonia, primary or influenzal	711	683	820	747
Poliomyelitis:				
Paralytic	15	14	15	22
Non-paralytic	4	3	8	7
Puerperal pyrexia and fever	221	244	279	281
Scarlet fever	1361	1137	1043	796
Smallpox	7	4	2	..
Typhoid fever	1	1	2	..
Whooping-cough	3004	2308	2800	2946

* Not including late returns.

Fluorine Tests on Kilmarnock Water-supply

The fluorine content of the drinking-water in Kilmarnock is being investigated in a preliminary survey which may lead to the addition of fluorine as a means of combating dental caries. A part of the population of 42,000 draws its water from the farmlands of the Fenwick area, and the remainder from the uplands of the Ayrshire-Renfrewshire border. The first samples taken from the two sources contained 0·28 and 0·12 parts per million of fluorine respectively. Children who have always lived in an area drawing water exclusively from one or other source are being examined to see whether the higher or lower fluorine content has had any noticeable effect on their teeth. When enough information has been collected about the present state of their teeth, it is proposed that the fluorine content of the water from the border uplands be raised to between 1·0 and 1·5 p.p.m., while the Fenwick water is unchanged. The health committee and the water committee have agreed to the plan in principle, but the details await their further decision. The cost of the addition is estimated at £3 a day, excluding the expense of the initial installation, but Dr. Bryce Nisbet, medical officer of health for the burgh, to whom we are indebted for these notes about the plan, thinks that this may be on the high side.

In a special article in this issue Lieut.-Colonel E. F. W. Mackenzie examines the evidence for and against the addition of fluorine to public water-supplies. He is in favour of its immediate adoption on a national scale.

Births, Marriages, and Deaths

BIRTHS

ADDERLEY.—On May 1, at King's College Hospital, to Edwina Jean (née Askew), wife of Dr. D. J. Adderley—a son.

ANCILL.—On April 30, at Bristol Maternity Hospital, to Sheilah Kendrick (née Parrott), wife of Dr. R. J. Ancill—a son.

AYLETT.—On April 28, at King's College Hospital, to Winsome, wife of Mr. Stanley Aylett, M.B.E., F.R.C.S.—a daughter.

BROOKS.—On May 4, at East Bridgford, Notts, the wife of Dr. Geoffrey Brooks—a daughter.

DAVEY.—On April 28, to June (née Pearson), wife of Dr. C. J. C. Davey—a daughter.

GILROY BEVAN.—On April 25, at the Queen Elizabeth Hospital, Birmingham, to Patricia Joan (née Laurie), wife of Dr. P. Gilroy Bevan—a son.

HAMILTON.—On April 21, to Ann, wife of Dr. W. S. Hamilton, 8, Norrey's Road, Cumnor, Oxford—a daughter.

HUGHES.—On April 27, at Forbes Fraser Hospital, Bath, to Mary (née Hillersdon) and Dr. William Hughes—a daughter.

LIVINGSTONE.—On April 29, at University College Hospital, to Mair (Dr. Thomas) wife of Mr. James Livingstone—a daughter.

MCCALL.—On April 28, to Joan (née Sale), wife of Dr. James McCall, of Kwambonambi, Zululand—a daughter.

MACLEOD.—On April 20, at St. Mary's Hospital, Portsmouth, to Marjorie, wife of Dr. Hugh Macleod—a daughter.

RAW.—On April 30, at Carshalton, to Margaret (née Trew), wife of Dr. John P. Raw, of 57, Benhill Avenue, Sutton—a son.

RAWLINS.—On April 27, at Bracken Lea Nursing Home, Twyford, near Winchester, to Diana, wife of Dr. J. S. Pepys Rawlins—a daughter.

SMITH.—On April 25, in Brooklyn, New York, to Hilda (née Walker), wife of Dr. J. F. S[illegible]

SPRIGGS.—On April 26 [illegible]s, to Sheila (née More), wife of Dr. [illegible]

TOWNSEND.—On April 2[illegible] Betty (née Stone), wife of Dr. W. H. Townsend—a son.

MARRIAGES

KERR—TYSON.—On May 3, at Urmston, Ian Hamilton Kerr, M.A., M.B., of Altrincham, to Esther Selkirk Tyson, B.A., of West Gate, Urmston.

REYNOLDS—WICKS.—On April 26, at Hampstead, David Farmer Reynolds, M.B., of Southfields, London, to Betty Theodora Wicks, of Melbourne, Australia.

ROOKE—OAKLEY.—On April 26, at Lancaster Gate, London, Geoffrey Basil Rooke, B.M., to Nancy Oakley.

DEATHS

COLLEN.—On April 27, at Ditchling Common, Burgess Hill, Edward Victor Collen, B.A., M.D. Dubl., aged 76.

CUTLER.—On April 28, at sea, Frederick John Cutler, M.R.C.S., of Hastings.

GRATTAN.—On April 30, at Hitchin, Col. Henry William Grattan, C.B.E., D.S.O., M.R.C.S., late colonel, R.A.M.C., late of Letchworth, aged 80.

PEARSON.—On May 2, at Dartford, Malcolm George Pearson, B.M. Oxfd.

STEVEN.—On April 29, at Ripon, Peter Alexander Steven, M.B. Glasg., aged 74.

TOWERS.—On April 29, Arthur Henry Tower, M.B. Edin., B.HY. Durh., D.P.H., of Brampt[illegible]

WALES.—On May 3, at South[illegible]ys Wales, M.A., M.B. Camb., late of [illegible], aged 75.

Obituary

JOHN PATON MacGIBBON

M.D. Edin., F.R.C.P.E., D.P.H., D.R.

Dr. J. P. MacGibbon, depute director of the radiodiagnosis department of Edinburgh Royal Infirmary, died on April 20 at the age of 48.

His father, the late Prof. John MacGibbon, held the chairs of midwifery and gynæcology in the Universities of the Witwatersrand and of St. Andrews.

MacGibbon studied medicine at the University of Edinburgh and also for a short time at Johannesburg, and he graduated M.B. in Edinburgh in 1929. Despite serious illnesses in childhood and adolescence which left him grossly crippled with extensive paralysis of the legs and severe kyphoscoliosis, he took a keen interest in sport and was awarded his Edinburgh rowing blue as cox. After holding house-appointments he took the M.R.C.P.E. and the M.D. with commendation in 1933. But he had already decided to take up radiology, and he obtained the diploma in radiology of his own university in 1935. Two years later he became F.R.C.P.E. He worked for the most part in the department of radiology in the Royal Infirmary, Edinburgh, and later he was appointed a depute director of the radiodiagnostic department as well as lecturer in radiodiagnosis in the University of Edinburgh.

A colleague writes: "Wee Mac" was a most courageous man for whom everyone had the highest respect and affection. As a radiologist he attained a high standing, but his diffident nature as well as the physical limitations of his strength restricted his efforts to the day-to-day work of his department, and he did not write much. His opinion was sought by all members of the staff, especially in cardiovascular disorders and congenital heart-disease. MacGibbon's teaching qualities were of the highest order and, combined with his close personal interest in his students, they won for him a quite extraordinary affection in a long series of radiologists and radiographers. In the Edinburgh School his cheerful presence, ready courtesy, and unvarying helpfulness were used to the full and were taken for granted. It will be difficult to fill his place both in his professional work and in the hearts of his many friends.

SIR MILSOM REES

M. J. S. writes: Milsom Rees had a remarkable career, but then he was a remarkable man. When he qualified, real surgery might be said to be in its infancy, and, with all due respect to Golden Square, ear, nose, and, throat surgery had hardly seen the light of day. He determined however to take up E.N.T. work as his specialty; but at an early stage in his career he abandoned what the physicians might call the more aggressive or destructive aspect of his specialty, and devoted himself almost entirely to conservative treatment. And what a success he made of it. Time came when he had for patients kings, queens, princes, and rulers, and others who, like himself, had won fame for themselves.

[Blake

His influence through his contacts was immense. Many of his patients became his friends, and the Royal Family had for him a special regard. King George V, when he was recuperating from his severe illness, looked forward to Milsom's visits. His Majesty evidently had great faith in Milsom's financial brain, for when his special nurse, "Blackie," of the London Hospital, consulted him about an income-tax form—the first she had ever received—the King replied "Give it to Milsom Rees, he will fix it for you."

For Rees the greatest singer was Melba. Her larynx and vocal chords were, he thought, the most perfect he had ever seen. The nearest approach, he thought, to her was Madam Flagstad. Of men he thought the greatest was Jean de Reszke. Among the politicians who were his patients his favourite was Arthur Balfour. Milsom always looked forward to his visits and gave him extra time so that he could enjoy the more of his company.

Probably Milsom's greatest friend was Alfred de Rothschild, who came to rely on Milsom more and more. Later St. Bartholomew's and other London hospitals benefited financially through this friendship, for Rees was made a trustee of de Rothschild's residuary estate, and from this charity was able from time to time to donate large sums of money.

It was only when I became his patient myself that I appreciated his real worth. He was renowned for his treatment of the larynx, but it is doubtful if anyone could equal his touch and gentleness in passing the eustachian catheter. His skill with this instrument, and his treatment of the middle ear, brought him patients from many lands, and many from his own profession, including his great friend, Lord Dawson.

What had impressed me before I knew Milsom was the fact—well known in golfing circles—that in competition at Royal St. George's, Sandwich, he had completed two rounds in a total of 144 strokes, and on the following weekend he holed the Old and New Courses at Sunningdale in a similar *number of strokes—four rounds of golf, on such courses, that* would have won the Open Championship for any professional golfer at the time. Later I learnt the reason for this proficiency. He had installed a golf-net in the garage at the back of his house in Wimpole Street, and there, in his spare time, he practised assiduously, aided and abetted by an assistant who had played golf for England, and who today is world-famous in another branch of surgery. Like every golfer he had his theories, and he gradually came to believe that the ulnar nerve *had all to do with putting.*

In later years Rees spent more and more of his time at his delightful home "Port Regis" which overlooks the sea near Broadstairs. Here he built a model preparatory school for boys, where the children of professional colleagues in straitened circumstances were awarded scholarships. Gradually he sought retirement. Occasionally during the war he came to Town to see old patients, but after the war he came no more, and those who knew him at his clubs, the Garrick, Sunningdale, and Walton Heath, thought he had passed on. In the last few years his health declined rapidly, but I am sure his friends will be glad to know that he died peacefully after an attack of pneumonia, almost on his 80th birthday.

Appointments

BIRCHALL, J. C., M.B. Lpool, D.P.H.: deputy M.O.H. and deputy school M.O., Croydon.

[illegible] C.S.: asst. chest physician (S.H.M.O.), Newport [illegible]uthshire H.M.C. group.

[illegible] Lond., M.R.C.P.: asst. chest physician (S.H.M.O.) [illegible] *and Sirhowy Valleys and part of the North* Monmouthshire H.M.C. groups.

* MOORE, JOHN, B.A., M.B. Dubl., D.A.: part-time consultant anæsthetist to hospitals in Liverpool.

PENNIE, J. D., M.B. Aberd.: appointed factory doctor, Golspie district, Sutherland.

RANGER, DOUGLAS, M.B. Lond., F.R.C.S.: asst. consultant laryngologist, London Chest Hospital.

TASKER, J. R., M.D. Camb., M.R.C.P.: consultant in general medicine, Northampton-Kettering area.

* Amended Notice.

Birmingham Regional Hospital Board:

HUTCHISON, J. T., M.B. Glasg., F.R.F.P.S.: asst. chest physician and medical director, Wolverhampton mass-radiography unit.

JENKINS, C. R., M.R.C.S., D.A.: part-time consultant anæsthetist, Shrewsbury group of hospitals.

MACARTNEY, J. N., M.B.E., M.D. Belf.: consultant chest physician, Walsall group of hospitals.

South Western Regional Hospital Board:

CROSS, E. G. W., M.R.C.S.: psychiatric registrar.

LONDON, P. S., M.B. Lond., F.R.C.S.: senior registrar in orthopædic and traumatic surgery, Bath clinical area.

LUKIANOWICZ, NARCYZ, M.D. Lwow: psychiatric registrar.

TAYLOR, A. W., M.B. Lond.: psychiatric registrar.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

EMERGENCY BED SERVICE.—In the week ended last Monday applications for general acute cases numbered 1030. The

Notes and News

DISTRIBUTION OF TERRAMYCIN

THE Ministry of Health, Department of Health for Scotland and ministry of health and local government for Northern Ireland announce that very limited supplies of terramycin will be available from May 12. For the present, hospitals will be allowed to use it for the treatment of any conditions in which they think it suitable; but its use for domiciliary treatment will be limited to the conditions for which aureomycin is supplied to practitioners—i.e., (1) suspected cases of ornithosis, (2) proved cases of undulant fever (brucellosis), (3) lymphogranuloma inguinale, and (4) severe cases of atypical pneumonia in which there is good reason to believe that the cause is a virus. An official statement says: "Terramycin, like aureomycin and chloramphenicol, is costly and its use can be justified only for conditions in which other drugs (e.g., sulphonamides or penicillin) are unlikely to be effective." Distribution will be through regional distribution centres, and issues will be made at the discretion of the doctors in charge of these centres. Most of the terramycin will be in tablet form (250 mg., 100 mg., and 50 mg. per tablet); but preparations such as intravenous, elixir, and oral drops will be available in extremely small quantities. Supplies for hospitals and patients outside the National Health Service will be obtainable from the centres on the understanding that the cost will be recovered by the Ministry of Health from the hospital or practitioner concerned. The centres are as follows:

Region	*Centre*
England and Wales:	
Newcastle	Chief Pharmacist, Newcastle upon Tyne General Hospital, 418, Westgate Road, Newcastle, 4. Tel. Newcastle 35211.
Leeds	Medical Superintendent, Leeds Blood Transfusion Laboratory, The Bridle Path, York Road, Seacroft, Leeds. Tel. Leeds 45091/3
Sheffield	Chief Pharmacist, City Hospital, Hucknall Road, Nottingham. Tel. Nottingham 63361.
East Anglian ..	Chie[illegible] Hospital, C[illegible]
North-West Metropolitan ..	Chie[illegible] Hospital, T[illegible] Hounslow 2311.
North-East Metropolitan ..	Medical Superintendent, Mile End Hospital, Bancroft Road, E.1. Tel. Advance 2873/5
South-East Metropolitan ..	Medical [illegible] Park Hospital, [illegible]en 1077/8.
South-West Metropolitan ..	Medical [illegible]don Blood Suppl[illegible], Sutton, Surre[illegible]
Oxford	Chief P[illegible] *Hospitals*, Oxford. Churc[illegible] Tel. Oxford 48051.
South Western ..	Medical Superintendent, Ham Green Infectious Disease Hospital and Sanatorium, Bristol. Tel. Bristol 31165.
Wales	Medical Superintendent, City Isolation Hospital, Canton, Cardiff. Tel. Cardiff 21166.
Birmingham ..	Medical Superintendent, Selly Oak Hospital, Birmingham. Tel. Selly Oak 1361.
Manchester ..	Chief Pharmacist, Manchester Royal Infirmary, Manchester, 13. Tel. Ardwick 3300.
Liverpool	Medical Superintendent, Aintree Hospital, Fazakerley, Liverpool, 9. Tel. Aintree 2321.
Scotland:	
Northern	Medical Superintendent, Raigmore Hospital, Inverness.
Eastern	Medical Superintendent, King's Cross Hospital, Dundee.
North Eastern ..	Dr. J. Smith, Regional Laboratory, City Hospital, Aberdeen.
South Eastern ..	(For general practitioners.) Medical Superintendent, Western General Hospital, Edinburgh. (For hospitals.) Chief Pharmacist, Western [illegible]urgh.
Western	(F[illegible] Senior Adminis[illegible] Western Regiona[illegible] [illegible] Regent Street, Glasgow. (For hospitals.) Chief Pharmacist, Centr[illegible] Infusion Fluids Laboratory, 112, Ingra[illegible] Street, Glasgow, C.1.
Northern Ireland:	Institute of Pathology, Grosvenor Road, Belfast.

DENTISTS REGISTER

THE Dentists Register for 1952, published at 18s. by Constable & Co. Ltd., 10, Orange Street, London, W.C.2, for the Dental Board of the United Kingdom, contains 15,5[illegible] names of dentists (including 218 dentists from the Dominions and Colonies and 272 foreign dentists) against 15,327 (including 122 dentists from the Dominions and Colonies and 277 foreign [illegible] in 1951

IN MEMORY OF ALMROTH WRIGHT

THE fifth anniversary of the death of Sir Almroth Wright was made the occasion for a gathering on April 30 of his old pupils and friends, together with the present scientific and senior technical staff of the Wright-Fleming Institute, to see the memorial display cabinet designed by Mr. J. D. Fyffe and constructed by Mr. G. H. Friese-Green, of Starkie Gardner Ltd., and to hear the oldest inhabitant, Dr. John Freeman, recount something of the life and character of "the Old Man." With a fund of reminiscences and anecdotes, Dr. Freeman portrayed the many-sided genius of his late chief, who was at his zenith in the years between the Boer War and the first world war, and who continued to work unrelentingly in his beloved laboratory until his death at the age of 85. Stories were told of his friendship with famous men in many walks of life—including Bernard Shaw, Arthur Balfour, and Lord Haldane; of the circumstances of his being knighted in order to get the typhoid vaccine accepted by the Army; of his famous letter to the *Times* on women's suffrage; of his "amazing asperities" and his incapacity to suffer fools gladly; and of how he eschewed the "voluptuary pleasures."

Besides his many scientific contributions and the development of the simple but ingenious apparatus based on the teat and capillary pipette which has found followers in many laboratories, Wright found time for a large consulting practice. He had many influential patients and it was with their help that he founded the Inoculation Department which developed into the present Institute. Indeed, Lord Iveagh, chairman of the Institute council and a generous benefactor, who presided over the gathering, claimed to be one of Sir Almroth's first patients for the vaccine treatment of boils.

The mahogany display cabinet, with its inscription "God offers to every mind its choice between truth and repose," is divided into four sections—antityphoid inoculation, vaccine therapy, treatment of wounds, and technical methods—representative of Wright's different scientific activities; and a centre-piece contains his notebook and evidence of some of the honours which came his way.

ANOTHER HOME FOR THE AGED SICK

> "There is not much point in learning to walk up and down stairs, if the only stairs one can use are the specially built ones in the hospital gymnasium; or in learning to manage a needle in a partially paralysed hand, if the only object is to make little mats in the occupational therapy classes."[1]

OLD people formerly went into hospital to die, or to lie abed for years; their successors can hope for active treatment and very often for considerable recovery of power and mobility. Yet, as King Edward's Hospital Fund point out in the booklet quoted above, many of them have no family home to go to, and they are no longer fit to live alone. Moreover the dividing line between health and sickness is a shadowy affair in age. They need easy access to a bed in a ward, as well as to a place where they can live a normal life; and it so happens that the National Health Service has failed to provide such a flexible arrangement.

The King's Fund, however, have begun to fill the gap by allocating £350,000 to set up homes attached to London hospitals with a well-developed interest in geriatrics. They have already opened six such homes, which receive patients who cannot benefit further from hospital treatment, yet who still need some nursing care, or who cannot immediately be sent home.

Greenfield, the sixth home, was opened on April 28 by the Countess of Limerick, vice-chairman of the British Red Cross Society. It is linked with the South-West Middlesex Hospital Management Committee, and the 36 patients in it are under the care of Dr. Marjory Warren, from whose wards in the West Middlesex Hospital they have graduated. The Middlesex branch of the British Red Cross Society, under the chairmanship of Mrs. D. Balsom, is responsible for running the home, which is on a pleasant freehold property at Ealing and has already developed a friendly atmosphere. The main house stands in its own garden, and the Fund has also rented on a long lease a semi-detached house which adjoins it. The total cost of purchase, repairs, and equipment has been £28,283. The maintenance costs of the patients—who have been in residence since February—are met by the North-West Metropolitan Regional Hospital Board, and there is a local committee of management.

The other homes so far provided by the Fund are Whittington, at Highgate, linked with the Archway Group of Hospitals; Westmoor, at Roehampton, linked with the Battersea and Putney Group; Fallowfield at Chislehurst, linked with the Orpington and Sevenoaks Group; The Gables, Blackheath, linked with the Woolwich Group; and Beechgrove, Sydenham Hill, linked with the Camberwell Group. Sir Ernest Pooley, in handing the home over to the British Red Cross Society, said that the Fund hoped to open thirteen such homes in all.

A NEW SPA HOSPITAL

> "Therefore the moon, the governess of floods
> Pale in her anger, washes all the air
> That rheumatic diseases do abound—"

IN quoting Titania, the Archbishop of York was illustrating an ancient recognition of the alliance between damp and rheumatics—though it is possible, of course, that Titania was thinking of colds in the head. Dr. Garbett was opening, on May 1, the White Hart Hospital at Harrogate, which is to be used, as an annexe to the Royal Bath Hospital, by patients needing spa treatment. The old hotel building, which still keeps Richard of Bordeaux's white hart above the door, has been acquired and equipped by the Leeds Regional Hospital Board at a cost of £96,000. It is decorated, after the modern fashion for hospitals, in light and airy colours, and pleasantly furnished. Fifty women patients are already in residence, and later men will be taken too; for there are beds for 133 in all. The outlay is thought to have been less than a third of what would have been needed to buy new premises, and the cost per bed, including furnishing and equipment, has worked out at about £830.

Rheumatism is still accepted by many people as the natural associate of age; and it is certainly among our most disabling and costly diseases. In the Leeds region alone, 30% of the patients treated for rheumatism are miners, and a further 30% are workers in other industries. We still know little about its treatment and still less about its causes; but the value of spa treatment in allaying pain and restoring mobility is well known; and Harrogate, as the Archbishop said, has always been a shrine for rheumatic pilgrims. The stimulating and cheerful atmosphere of the new hospital should lift the spirits of the patients while the physiotherapy department is limbering up the joints.

PHARMACISTS AND THE METRIC SYSTEM

A PRODUCTIVITY team representing the pharmaceutical industry in this country visited the U.S.A. in 1950 to investigate the preparation of pharmaceutical products for the market. The Association of British Pharmaceutical Industry set up a committee to consider the team's report, and the committee's recommendations were presented to the annual general meeting of the association on April 23.

The committee would like to see more collaboration between manufacturers on packaging problems, and the adoption of standard containers for the supply of drugs to pharmacists. Accordingly they advise that all liquid galenicals should be sold by volume instead of by weight, and that solids, liquid galenicals, and pharmaceutical chemicals should be sold by metric weights and measures. They would not change the packing of such things as camphorated oil and Epsom salt, which are made up ready for resale over the counter. The products affected are largely those which the pharmacist buys in bulk for dispensing.

Such changes would, it is claimed, considerably reduce the number of bottle sizes, and so make bottles cheaper and easier to get. Moreover, storage space could be less, and standard packing-cases more widely used. The recommendations may be put into practice in the spring of next year.

Scottish Regional Hospital Boards

Mr. J. D. Macrae and Mr. G. A. Wright have been appointed to the two remaining vacancies in the Northern Regional Hospital Board.

One of the two remaining vacancies in the South-Eastern Region has been filled by the appointment of Lieut.-Colonel A. N. Balfour.

Register of Biological Consultants

The Institute of Biology has recently established a Register of Biological Consultants. Subjects covered by biologists on the register include agronomy, bacteriology, biochemistry, ecology, entomology, fisheries, forensic biology, histology, microbiology, nutrition, pest control, protozoology, river pollution, and wild-life conservation. The institute can now recommend specialist advisers in any branch of the biological sciences. Inquiries should be sent to the general secretary of the institute, Tavistock House South, Tavistock Square London, W.C.1.

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[1] Care of the Aged Sick. Published by King Edward's Hospital Fund for London, 10, Old Jewry, London, E.C.2. Pp. 15.

Queen's University Club, London

The annual dinner of this club will be held at the Rembrandt Hotel, South Kensington, on Thursday, May 29, at 7 P.M. Tickets may be had from the hon. secretary of the club, Mariga, Arkley, Barnet, Herts.

Association of Scientific Workers

The London optical practitioners' branch of the association is holding a film show for optical practitioners and ophthalmologists at 7.30 P.M. on Friday, May 16, in the College of Preceptors, 2, Bloomsbury Square, W.C.1. Further information may be had from Mr. W. B. Bland, 26, Cambridge Road, Ilford, Essex.

Broadmoor Institution

Dr. S. G. James has been appointed superintendent of Broadmoor Institution, in succession to Dr. J. S. Hopwood who is retiring after 27 years' service at the institution.

Dr. James graduated M.B. at the University of Sydney in 1926. After holding resident appointments at Sydney Hospital he came to this country and became senior house-physician at the West End Hospital for Nervous Diseases, London. He took the M.R.C.P. in 1931 and the D.P.M. three years later. He held the posts of assistant medical officer at Friern Hospital and of deputy superintendent to the Rampton State Institution, Retford, before he took up his present appointment as superintendent of Moss Side Hospital, Maghull. He is also physician to the Liverpool psychiatric clinic.

Royal Society

The following have been elected foreign members of the society:

SVEN HÖRSTADIUS, professor of zoology, in the University of Uppsala, for his work in experimental embryology of animals of many types;

ALBERT JAN KLUYVER (Delft) for his contributions to the comparative biochemistry of micro-organisms and the stimulus he has given through his pupils to microbiology in a number of countries;

ALBERT MARCEL GERMAIN RENÉ PORTEVIN (Paris) for his contributions to the science of ferrous and non-ferrous metallurgy and their applications to industry;

TADEUS REICHSTEIN (Basle) for his investigations on cardiac poisons and adreno-cortical hormones.

Medical Awards

The following awards have been made to R.A.M.C. officers for services in Korea:

M.B.E.—Major W. G. Miln, M.R.C.S.

Mentioned in Despatches.—Lieut.-Colonel A. Maclennan, O.B.E., M.B.; Captain P. M. Bretland, M.B.

Scottish Society of Anæsthetists

The following office-bearers have been elected for 1952-53: president, Dr. T. J. C. MacDonald; vice-president, Dr. W. E. Shearer; hon. secretary, Dr. R. N. Sinclair; other members of the executive council, Dr. H. H. Pinkerton, Dr. J. D. Robertson, Dr. H. W. C. Griffiths, Dr. A. G. Miller, Dr. A. Tindal, Dr. J. W. L. Bain, and Dr. M. Muir.

Medical Superintendents' Society

The annual general meeting of this society will be held at the City Hall, Cardiff, on Wednesday, May 14, at 5 P.M. The annual dinner will be held in the Park Hotel, Cardiff, on Friday, May 16, at 7 P.M. On May 15, at 10.15 A.M. there will be a joint meeting with the Royal Medico-Psychological Association, when Miss Patricia Hornsby-Smith, parliamentary secretary to the Ministry of Health, will take part in a discussion on Hospitals and the State.

Society for Endocrinology

The following officers and members of committee have been elected: chairman, S. J. Folley; honorary secretaries, C. H. Gray and N. F. Maclagan; honorary treasurer, F. L. Warren; editor of society's *Proceedings*, S. Zuckerman; members of committee, E. C. Amoroso, G. W. Harris, C. J. O. R. Morris, and S. L. Simpson. Communications should be sent to the hon. secretary of the society, Department of Chemical Pathology, King's College Hospital, London, S.E.5.

Dr. Alexander MacGregor will visit Yugoslavia and Italy this month to lecture for the British Council on recent advances in British dental surgery.

Diary of the Week

MAY 11 TO 17

Monday, 12th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Prof. [illegible] ion Problem in Calciu[illegible] n Men and Rats.
MEDICAL SOCIE[illegible], W.1
8.30 P.M. Sir [illegible] icine?
ROYAL EYE HO[illegible]
5 P.M. Dr. T. [illegible] on.
INSTITUTE OF [illegible] Denmark Hill, S.E.5
5.30 P.M. Dr. E. Stengel: Lecture-demonstration.

Tuesday, 13th

ROYAL EYE HOSPITAL
5 P.M. Prof. Arnold Sorsby: Genetics in Ophthalmology.
ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Dr. J. G. Scadding: Diagnosis of Early Pulmonary Tuberculosis.
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School, W.2
5 P.M. Prof. W. I. B. Beveridge, D.V.SC.: Some Aspects of Immunity to Virus Diseases.
CHADWICK LECTURE
2.30 P.M. (26, Portland Place, W.1.) Dr. E. L. Sturdee: Food and Health.

Wednesday, 14th

NEWSHOL[illegible]
6 P.M. [illegible] Hygiene, Keppel Street, W.C.1.) [illegible] F.R.S.: Medical Research—Its [illegible] d Social Significance. (First of three lectures.)
INSTITUTE OF DERMATOLOGY, St. John's Hospital, W.C.2
5.30 P.M. Dr. C. W. McKenny: X-ray Technique.
POSTGRADUA[illegible] SCHOOL OF LONDON
11.45 A.M. [illegible] conference.
MANCHESTER [illegible]
4.30 P.M. [illegible] versity of Manchester.) Dr. [illegible] Pathologist.
UNIVERSITY OF GLASGOW
8 P.M. (Department of Ophthalmology.) Dr. J. N. Tennent: A Visit to India.

Thursday, 15th

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1
7.30 P.M. Mr. J. Carmichael, D.SC.: Animal-man relationship in Tropical Diseases in Africa.
NEWSHOLME LECTURE
6 P.M. (London School of Hygiene.) Sir Edward Mellanby: Medical Research. (Second of three lectures.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. Charles Fletcher: Observer Error in Clinical Medicine.
INSTITUTE OF PSYCHIATRY
3 P.M. Prof. R. B. Cattell (University of Illinois): Integration of Research on Personality Factors.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W.1
5 P.M. Dr. J. H. Paterson: Neurology lecture-demonstration.
WEST END HOSPITAL FOR NERVOUS DISEASES
5.30 P.M. (Department of Psychiatry, 48, Cosway Street, [illegible]) Dr. E. A. Bonnet: Psycho- [illegible] (First of two lectures.)
BRITISH [illegible], Welbeck Street, W.1
8 P.M. [illegible] dies in Optimum Dosage.
LONDON [illegible] OCIETY
8.30 P[illegible] .1.) Dr. S. L. Simpson: [illegible]
UNIVERSITY OF EDINBURGH
10 A.M. (University New Buildings, Teviot Place.) Dr. Alfred Blalock (Baltimore): Lecture.
HONYMAN GILLESPIE LECTURE
5 P.M. [illegible] ngs, Teviot Place.) Dr. Catherine [illegible]
UNIVERSI[illegible]
5 P.M. [illegible] Wynd, Dundee.) *Prof. W. C. W. Nixon*: Uterine Action—Normal and Abnormal.
UNIVERSITY OF DUBLIN
4.30 P.M. (School of Physic, Trinity College.) Prof. S. P. Bedson, F.R.S.: The [illegible] Group of Viruses and its Bea[illegible] s Pneumonia and other Prob[illegible] ecture.)

Friday, 16th

FACULTY OF RADIOLOGISTS
3.30 P.M. (Royal College of Surgeons, Lincoln's Inn Fields, W.C.2.) Dr. H. R. Sear (Sydney): Congenital Bone Dystrophies and their Correlation. (Skinner lecture.)
NEWSHOLME LECTURE
6 P.M. (London School of Hygiene.) Sir Edward Mellanby: Medi[illegible] e lectures.)
POSTGRADUAT[illegible] ON
11.15 A.M. [illegible] conference.
4 P.M. Dr. [illegible] Dust-inhalation on the Lungs.
INSTITUTE OF CHILD HEALTH
5 P.M. (The Hospital for Sick Children, Great Ormond Street, W.C.1.) Prof. Arvo Ylppö (Helsinki): Respiratory Disturbances in Newborn and Premature Infants.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. G. Cochrane: Clinical demonstration.
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
2 P.M. (Queen Charlotte's Maternity Hospital.) Mr. H. Malkin: Cæsarean Section.
UNIVERSITY OF BIRMINGHAM
4 P.M. (Faculty of Medicine.) Prof. Hans Selye (Montreal): The General Adaptation Syndrome.

Saturday, 17th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
11.30 A.M. Dr. J. J. Pressman (Los Angeles): Replacement of Resected Cervical Trachea.

TREATMENT OF DIABETIC KETOSIS

J. D. N. Nabarro
M.D. Lond., M.R.C.P.

A. G. Spencer
G.M., M.D. Lond., M.R.C.P.

J. M. Stowers
M.B. Camb., M.D. Harvard, M.R.C.P.

From the Medical Unit, University College Hospital Medical School, London

Although severe ketosis is not an uncommon complication of diabetes, there is still no general agreement about the best method of treatment. The chief points at issue relate to insulin dosage, alkali therapy, the value of the early administration of glucose, and the necessity for giving additional potassium, magnesium, and phosphate.

In theory these problems could be settled by comparison of the results obtained in parallel series of cases treated by various methods, but assessment of the severity of cases of diabetic ketosis is extremely difficult (Himsworth 1949), and a large number of patients would be required.

Alternatively these therapeutic problems could be solved by a better understanding of the biochemical disorders which arise in diabetic acidosis and which have to be corrected in the course of treatment. The suggestions made here are based on an assessment of the metabolic disturbances, derived from data obtained in balance studies done on patients during recovery from ketosis (Nabarro et al. 1952).

These studies have been supplemented by investigations of various related metabolic problems, and by reference to the extensive literature on the treatment of diabetic ketosis. The methods have been evolved in the course of observation and treatment of 70 cases admitted to this hospital during the last six years. In 1947 a team was formed to investigate and treat all cases of diabetic ketosis admitted to this unit, and in the last four years 18 severe and 40 moderately severe cases have been treated. In this series there was one death—in a patient with advanced coronary artery disease who was admitted with moderately severe ketosis and perforated a duodenal ulcer thirty-six hours after the diabetes had been brought under control.

The syndrome of diabetic ketosis or acidosis is well known, but the terms diabetic ketosis, pre-coma, and coma are often used indiscriminately and without definition. In assessing the severity of any one case many factors must be considered (Collen 1942), and no rigid scheme is entirely satisfactory. We have followed Joslin (1946) in regarding any case with an initial plasma carbon dioxide combining power of less than 20 volumes per cent. as one of severe ketosis.

A full discussion of the total metabolic disorder in diabetic acidosis is contained in previous papers (Atchley et al. 1933, Butler et al. 1947, Nabarro et al. 1952). Briefly, ketosis is associated with a severe loss of body-water and electrolytes, both because partly neutralised keto-acids are excreted by the kidney and because heavy glycosuria produces osmotic diuresis. Typical losses are: from the extracellular fluid, water 3000 ml., sodium 500 m.eq., chloride 400 m.eq.; and from the cells, water 3000 ml., potassium 350 m.eq., phosphate 150 m.eq., and magnesium 40 m.eq. Effective therapy must not only restore normal carbohydrate metabolism, but also create conditions favourable for the replacement of losses both from the cells and from the extracellular fluid. These and other factors are considered in detail in relation to specific methods of treatment.

INSULIN

Diabetic ketosis results from either a lack of insulin or a failure of insulin action. The early administration of effective doses of insulin is the keystone of successful therapy. In a severe case the outcome often depends on the amount of insulin given in the first few hours. In Joslin's clinic this has been shown by comparing two large series (Root 1945). In one, given an average of 83 units in the first three hours, the mortality-rate was 12%; in the second, given 216 units, it was 1·6%. In our last 10 severe cases the average amount given in the first three hours was 160 units.

The main factors which should be considered in deciding insulin dosage are the normal insulin requirement and the severity of the acidosis, dehydration, and infection, all of which increase insulin resistance (Guest 1949). In the past there has been a tendency to give too little insulin initially. In a case of moderate severity we give 100 units of soluble insulin as an initial dose. When the patient's normal insulin requirement exceeds 60 units a day, or in the presence of a severe infection, severe dehydration, circulatory collapse, or coma, 200 units is more suitable. Blood is taken for blood-sugar estimation as soon as the patient reaches hospital. The initial dose of insulin is given without awaiting the result of this estimation, but this should be available in 30 minutes; and, if it is more than 600 mg. per 100 ml., we immediately give a further 100 units of insulin. The danger of producing hypoglycæmia with this dosage is negligible except in previously untreated diabetics and children, for whom smaller initial doses are advisable. Speed is so essential that in a severe case, provided the diagnosis has been established, the patient's own doctor should give 100 units of soluble insulin before sending the patient to hospital.

In the early stages of treatment the circulation is often poor and absorption of insulin may be delayed. The subcutaneous route is unsatisfactory in these circumstances, and we give four-fifths of the dose intramuscularly and a fifth intravenously. If the dose is very large, the intramuscular portion may be divided and given at several sites. It has been recommended that the whole of the early doses should be given intravenously to avoid depot formation and subsequent hypoglycæmia (Black and Malins 1949). Lawrence (1949) considers that large doses of insulin given intravenously have comparatively little effect on the blood-sugar. In rabbits a considerable proportion may be lost in the urine (Bruger and Friedman 1938), but this has not been confirmed in man (Mirsky et al. 1948). Pancreatic hyperglycæmic factor is present in many commercial insulins, and its effect may be apparent with intravenous administration of large doses (Bruch 1950). The use of small doses of P.Z. insulin in addition to the larger doses of soluble insulin introduces complicating factors in therapy without any definite benefit (Joslin 1946).

There is little agreement about how soon further insulin should be given or how the optimal dose should be assessed. Intervals ranging from 15 minutes to four hours have been advocated. The shorter ones do not allow time for the benefit of previous treatment to become apparent, and the longer ones carry the risk of serious undertreatment. If the insulin dose has been adequate, a fall in the blood-sugar level should be apparent within 90 minutes; and, if blood is taken for blood-sugar estimation at that time, the result will be available to guide the physician in deciding a suitable dose to give two hours after the original injection. If it is found that the blood-sugar level has risen, double the original dose is given. If it is approximately unchanged, the same dose is repeated; whereas if it is falling, no insulin is given but a further estimation is done 90 minutes later. We repeat the blood-sugar estimations at two-hour intervals and give a suitable dose of insulin as each result is obtained. Urine sugar tests give no indication of the blood-sugar level, when this is above 300 mg. per 100 ml., and cannot be relied on as a guide to insulin dosage; urinary tests for ketones have in our experience proved equally unsatisfactory for this purpose. When the blood-sugar level approaches the renal threshold, blood-sugar estimations may be discontinued. Specimens of urine are then obtained every three or four hours, and the dose of insulin is adjusted according to the amount of glucose found.

The blood-sugar levels and insulin dosage in a typical case of severe ketosis are shown in fig. 1*a*, and in fig. 1*b* the corresponding figures in a frail old lady, aged 73, with very severe ketosis resulting from insulin resistance of an allergic type. Such large doses of insulin are not often needed and can only be used with safety if frequent blood-sugar estimations are made.

RESTORATION OF EXTRACELLULAR FLUID

Depletion of extracellular fluid leads to circulatory collapse and extrarenal uræmia, and must be corrected as soon as possible by the administration of water, sodium, and chloride. The retention of extracellular electrolyte during recovery in 7 cases is shown in fig. 2. Sodium and chloride were found to be retained in the ratio of 1·3 m.eq. of sodium to 1·0 m.eq. of chloride, and this probably represents the optimal ratio for their administration in the early stages of treatment. Solutions with sodium and chloride in this ratio contain a proportion of lactate or bicarbonate, and contribute to the correction of the acidosis.

There is evidence to suggest that acidosis reduces carbohydrate tolerance (Haldane et al. 1924), interferes with the action of insulin (Mackler et al. 1951), impairs the cerebral oxygen utilisation (Kety et al. 1948), lowers the blood-pressure (Lange et al. 1951), and increases cellular katabolism. Attempts are sometimes made to correct the acidosis rapidly by giving large amounts of sodium lactate or bicarbonate. Formulæ have been proposed for the amount to be given based on the carbon dioxide combining power (Guest 1949); this is, however, an uncertain guide to the blood pH (Kety et al. 1948), and the formulæ, which take no account of varying renal compensation, have proved of little value. Further, it seems unreasonable to try to correct an over-all body acidosis by the administration of sodium, a base that is mainly extracellular. Even with modest use of lactate large amounts of sodium may enter the cells (fig. 6) and, as the ketonæmia diminishes, alkalosis may result (Harwood 1951). For these reasons we consider that sodium lactate and bicarbonate should be given with caution, and the ratio of sodium to chloride in the solution we use is equal to that in the extracellular fluid water (1·3 : 1).*

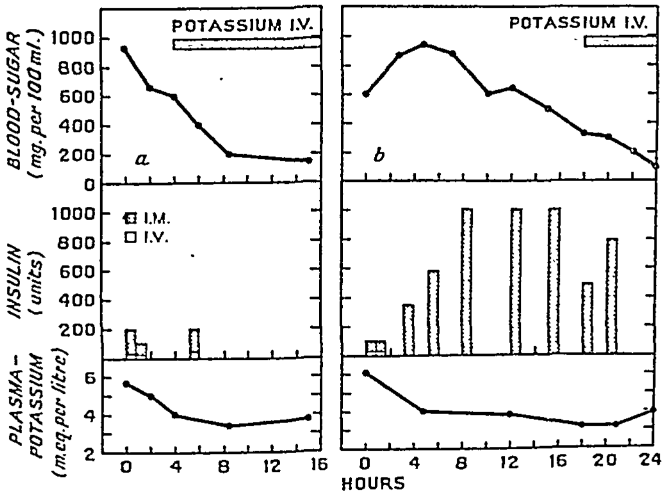

Fig. 1—Treatment of diabetic ketosis, showing control of insulin dosage by blood-sugar levels, and relation between plasma-potassium and blood-sugar levels in: *a*, typical severe case (case 1); *b*, in very severe case associated with insulin resistance (case 2) and in which intravenous insulin provoked widespread urticaria and was discontinued after two injections.

Plasma normally contains about 142 m.eq. of sodium and 103 m.eq. of chloride per litre. In many cases of diabetic ketosis the levels of sodium and chloride in the plasma are reduced. In very severe cases, despite an absolute deficit of sodium and chloride, the plasma levels may be raised. This results from the patient becoming too drowsy to take fluid by mouth while continuing to lose water in the urine and through hyperpnœa. Treatment cannot be delayed while electrolyte levels are determined, and a solution must be available that is suitable for all cases. We consider that in the initial stages of rehydration a satisfactory solution is one containing sodium 130 m.eq. per litre, chloride 100 m.eq. per litre, and lactate 30 m.eq. per litre.† Butler (1950) has recommended a more dilute solution because of the cellular water deficit. Our metabolic studies have shown that water is rapidly taken up by the cells as the blood-sugar level falls in the early stages of treatment, and hypotonic solutions will facilitate this process, but unless administered very rapidly their use may delay the full restoration of the extracellular fluid. Physiological saline solution contains 154 m.eq. each of sodium and chloride per litre. The concentration of chloride is in excess of that in the extracellular fluid and will tend to accentuate the acidosis; but, if renal function is adequate, this tendency is rapidly corrected. Isotonic saline solution, although often successful in practice, is theoretically not the best solution for severe cases.

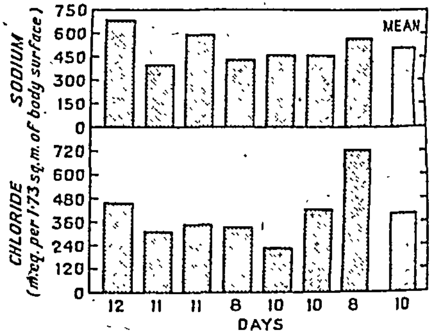

Fig. 2—Total retention of sodium and chloride during recovery from diabetic acidosis in seven patients.

At an early stage a decision must be reached regarding the route by which fluid is to be given. If there is nausea or any history of vomiting, oral administration is seldom successful. Gastric atony is often present, and after two or three hours several pints of fluid may be regurgitated, with grave risk of aspiration. Except in patients with mild ketosis rehydration should be by the intravenous route, and in severe cases the insertion of a cannula or plastic tube into a vein of the forearm is preferable to the use of a needle. In the presence of circulatory collapse it is difficult to get a satisfactory infusion running with a needle, and restlessness often leads to its dislodgement. Occasionally a subcutaneous infusion with hyaluronidase may prove satisfactory, but it should not be relied on in a severe case or when the peripheral circulation is not well maintained. The first litre of repair solution should be given rapidly and about two litres in the first 60 minutes. The rate of administration should be adjusted according to the age of the patient and the condition of the heart and lungs. A further litre may be given more slowly until conditions justify changing to a solution suitable for cellular restoration. The indications for this are discussed below.

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* Normally the concentration of sodium is about 142 m.eq. per litre in the plasma and extracellular fluid water: the concentration of chloride is 103 m.eq. per litre in the plasma and 115 m.eq. per litre in the extracellular fluid water.

† "Saline lactate solution": sodium chloride 5·85 g., sodium lactate 3·36 g., distilled water to 1 litre.

In some cases circulatory collapse may be present or develop in the course of treatment. Frequent clinical examination of the temperature of the extremities and measurement of the blood-pressure will enable this to be recognised quickly. Blood-transfusion is the best method of combating this complication; plasma infusion, although theoretically preferable, should at present be avoided because of the risk of homologous serum jaundice.

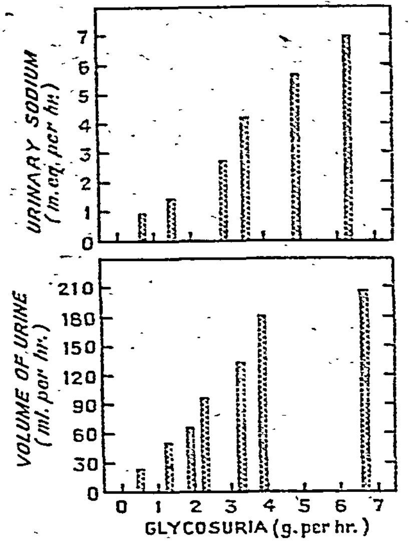

Fig. 3—Correlation between glycosuria, volume of urine, and urinary excretion of sodium in diabetic ketosis. Correlation coefficient glycosuria : volume 0·73 ± 0·06 ; glycosuria : sodium loss 0·68 ± 0·07.

RÔLE OF GLUCOSE

All authorities agree that glucose should be generously given from two to six hours after the start of treatment, by which time the blood-sugar level has usually begun to fall. Yet controversy continues over the value of the routine administration of glucose from the beginning of treatment, when the blood-sugar level is still high. Joslin (1946), Lawrence (Oakley 1949), Graham (1950), Butler (1950), and Thorn and Forsham (1950) believe that usually glucose should not be given at this stage, whereas Danowski et al. (1946), Soskin and Levine (1946), and other workers apparently continue to recommend it.

The evidence in favour of the early use of glucose in the treatment of diabetic acidosis may be summarised as follows. Himsworth (1932) clearly demonstrated that the administration of glucose decreased ketosis, and also that carbohydrate utilisation was increased by hyperglycæmia. This work has been confirmed by Mirsky et al. (1937, 1941), Soskin and Levine (1937, 1944), Wierzuchowski (1936, 1937), and Peters (1945, 1946). Himsworth found that most patients in diabetic acidosis recovered rapidly when treated from the beginning with glucose covered with insulin, provided that the depletion of body-water and electrolytes was also corrected.

Nevertheless there is now important additional evidence, both in relation to carbohydrate metabolism and to the interrelated problems of cell osmolarity and body hydration, which suggests that it is better to withhold glucose while the blood-sugar level is still high. Sound practical reasons lend support to these theoretical considerations. Although the rate of utilisation of glucose is increased by hyperglycæmia, there is an optimal level of blood-sugar at about 500 mg. per 100 ml., above which there is no significant increase either in the rate of peripheral oxidation of glucose or in glycogen storage (Root and Carpenter 1943). Franks et al. (1947) have evidence that it may actually decrease at these high levels.

The serious osmotic consequences of maintaining a high blood-sugar level in diabetic acidosis have recently been demonstrated by Seldin and Tarail (1950) and by Nabarro et al. (1952). Hyperglycæmia produces cellular dehydration and a continuing osmotic diuresis, with excessive loss of water, glucose, and sodium chloride in the urine (fig. 3). In severe ketosis, when the patient is profoundly dehydrated, this uncontrolled renal drain of water and electrolytes delays the restoration of body-fluids, even when there is intensive parenteral therapy. Under such conditions the patient's circulatory efficiency, already gravely impaired, is still further reduced, and the early use of intravenous glucose-containing solutions may in fact lead to the development of irreversible shock (Franks et al. 1947).

No discussion of the value of the early administration of glucose is complete without a reference to the cellular transfers of potassium and phosphorus which inevitably accompany changes in carbohydrate metabolism. Greenman et al. (1949), Nabarro et al. (1952), and others have shown that there may be a rapid fall in the plasma-phosphorus and plasma-potassium levels, because these ions are transferred into the cells when glycogen and organic phosphates are resynthesised. These transfers are increased by large infusions of exogenous glucose, and dangerously low plasma-potassium levels have often been recorded, with typical symptoms (Holler 1946) and sometimes with death (Nicholson and Branning 1947). Since the deposition of glycogen is part of the process of recovery, the associated development of hypokalæmia should not be used as an argument against the early administration of glucose, but should rather be an indication for the more effective use of potassium.

Besides these theoretical considerations there are two practical reasons against the early administration of glucose: the excellent results obtained when it is withheld and the greater precision by which insulin action may then be judged.

CELLULAR RESTORATION

Metabolic disturbances associated with the development of diabetic ketosis lead to profound alterations in the biochemical structure of the cells. Water is lost in the course of generalised dehydration, and protein is broken down as a consequence of the dehydration, relative starvation, and gluconeogenesis. Cellular electrolytes are lost, through breakdown of organic phosphates and glycogen, because of protein katabolism and because pH changes alter the base-binding power of the cell proteins. Large amounts of potassium, magnesium, and phosphate leave the cells and are excreted in the urine. If, as not infrequently happens, extrarenal factors have led to a depression of kidney function, the rate of release from the cells may exceed that of excretion (McCance and Lawrence 1935), and an apparent paradox will then arise in which high plasma levels of potassium, phosphate, and magnesium are found in association with an over-all body deficiency of these ions. When treatment starts, these electrolytes move back into the cells, and the plasma levels fall sharply. Continuing loss of potassium in the urine may also occur and lead to severe hypokalæmia (fig. 4). The accompanying table shows the levels of blood-urea and certain plasma-electrolytes in a recent series of 12 cases of severe ketosis.

Cellular repair after severe diabetic ketosis is a lengthy process. Water is taken up comparatively rapidly,

BLOOD-UREA AND PLASMA POTASSIUM, INORGANIC PHOSPHATE, AND MAGNESIUM LEVELS IN DIABETIC KETOSIS
(Magnesium levels were only determined in 2 cases)

—	Before treatment				After treatment (3–6 hr.)		
	Blood-urea (mg. per 100 ml.)	Plasma-potassium (m.eq. per litre)	Plasma-phosphate (mg. per 100 ml.)	Plasma-magnesium (m.eq. per litre)*	Plasma-potassium (m.eq. per litre)	Plasma-phosphate (mg. per 100 ml.)	Plasma-magnesium (m.eq. per litre)
Mean	63	5·7	3·9	—	3·5	2·3	—
Range	39–93	5·1–6·5	2·8–4·6	4·0–5·8	2·4–4·3	1·3–3·4	1·7–1·9

* Normal plasma magnesium 2 m.eq. per litre.

electrolytes are largely replaced during the first ten days of treatment, but protein restoration begins only after a latent period of some days and probably takes several weeks (Nabarro et al. 1952). Some indication of the cellular dehydration and magnitude of the electrolyte deficiencies is given in fig. 5, which shows the amount of water taken up by the cells in the first three days of treatment and the cellular electrolytes taken up in ten days. Metabolic studies during recovery afford only an incomplete picture of the losses that have occurred; but it has, for example, been shown that as much as 14 m.eq. of potassium per kg. of body-weight may be retained during the first ten days' treatment.

Evidence is accumulating that alterations of cellular electrolyte levels interfere with phosphorylation enzyme systems (Lardy and Ziegler 1945) and with carbohydrate metabolism in the liver (Buchanan et al. 1949), muscle, and brain (Lipsett and Crescitelli 1950). Cellular electrolytes should be offered at an early stage in treatment; this will not only hasten restoration of the cells but also lessen the fall of plasma levels that follows the administration of insulin and sudden reversal of cellular breakdown. Solutions containing electrolytes for cellular repair cannot safely be given at the start of treatment, because at that time the plasma levels of potassium, phosphorus, and magnesium are often high, and hyperkalæmia may lead to auricular standstill, heart-block, and cardiac arrest (Finch and Marchand 1943). Electrocardiograms suggesting severe potassium intoxication have been reported in untreated diabetic ketosis (Finch et al. 1946, Bellet et al. 1950), and in one case sudden death took place before treatment could be started (Neubauer and Frelick 1950). Insulin and replacement of the extracellular fluid soon lead to a fall of the plasma levels of potassium, magnesium, and phosphorus (see table); when this happens, a solution for cellular repair should be given intravenously. Plasma-potassium estimations can only be done rapidly with a flame photometer (Spencer 1950), and this will not always be available. However, provided there is a satisfactory urinary flow, it may safely be assumed that, when the blood-sugar level begins to fall, the plasma-potassium level will be showing a similar trend (fig. 1). In practice, therefore, as soon as the hyperglycæmia begins to diminish, intravenous therapy may be continued with a solution containing potassium, phosphate, and magnesium.

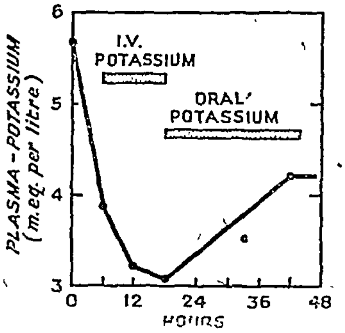

Fig. 4—Plasma-potassium levels during treatment of diabetic ketosis, showing moderate hypokalæmia despite administration of potassium (60 m.eq. I.V.; 90 m.eq. by mouth).

Potassium is the cellular electrolyte most urgently required by these patients. Cellular depletion of potassium and low plasma-potassium levels may lead to muscular paralysis and electrocardiographic changes. Since Holler's (1946) original account a further 20 cases of hypokalæmic muscular weakness with respiratory paralysis complicating the treatment of diabetic ketosis have been published (Frenkel et al. 1947, Nicholson and Branning 1947, Harvey 1948, Logsdon and McGavack 1948, Tuynman and Wilhelm 1948, Danowski et al. 1949, Nicholson and Spaeth 1949, Stephens 1949, Martin et al. 1950). Most of these patients had intravenous glucose in the early stages of treatment, with continuing diuresis; none had received potassium-containing solutions. Potassium depletion is also known to be associated with atony of the gastro-intestinal tract (Webster et al. [illegible] 1950); it is not unlikely that the gastric dilatation often present in patients with diabetic ketosis arises in this way. The early administration of potassium-containing solutions has led to a reduction in the incidence of this complication in our cases, and there has been less nausea and vomiting during the recovery phase. Cellular potassium depletion is also associated with abnormally high levels of cell sodium (Darrow and Pratt 1950). In untreated diabetic ketosis there is deficiency of both sodium and potassium; and if sodium is restored first, a considerable proportion enters the cells. Fig. 6 indicates the apparent accumulation of excess sodium in the cells and shows how the administration of potassium supplements will prevent it.

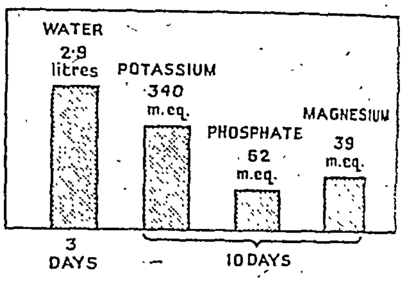

Fig. 5—Recovery from diabetic ketosis, showing increase of cell water in first three days and cellular electrolytes in first ten days, plotted in proportion to normal cellular composition (means of 5 cases corrected to standard body-surface 1·73 sq. m.).

Now that the great importance of potassium therapy has become widely recognised, [illegible] solutions are often given intrav[illegible] than ever, that the potential hazards should not be forgotten. Solutions containing 150 m.eq. of potassium per litre have been used (Nadler et al. 1950) but require continuous supervision, because the normal total potassium content of the extracellular fluid is only 70 m.eq. and, if the infusion suddenly flows rapidly, dangerous hyperkalæmia and cardiac arrest may develop. For routine administration a solution containing potassium 30 m.eq. per litre given not faster than 1 litre in four hours can safely be used. It should further be emphasised that intravenous potassium therapy must not be given unless the urinary output is well maintained (at least 50 ml. an hour).

The classical studies of Atchley et al. (1933) showed that considerable amounts of phosphorus were lost during the development of diabetic ketosis, but that during recovery phosphorus was restored less rapidly than potassium. In the course of treatment plasma levels of inorganic phosphorus may fall considerably, and phosphates may almost disappear from the urine. Phosphate plays an important rôle in carbohydrate metabolism and should therefore be included in the cellular repair solution. The concentration of phosphate that can be given by intravenous infusion is limited by possible

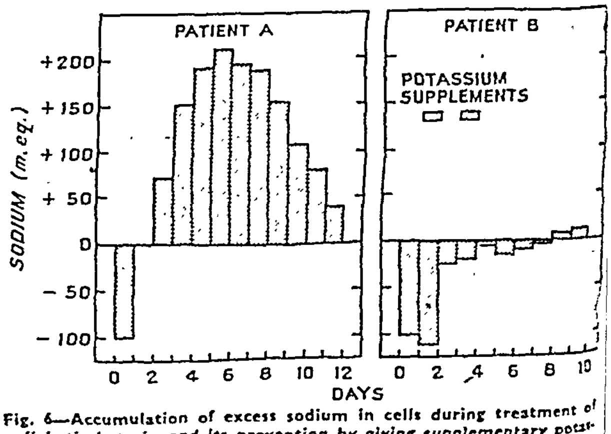

Fig. 6—Accumulation of excess sodium in cells during treatment of diabetic ketosis, and its prevention by giving supplementary potassium. Patient A received potassium in parenteral solution and diet. Patient B was given an additional 240 m.eq. by mouth.

urbance of calcium metabolism and the production of etany (Kjerulf-Jensen et al. 1951).

The development of diabetic ketosis is accompanied by considerable losses of magnesium, and plasma-magnesium levels fall in the course of treatment. Although it is known that magnesium is necessary for the efficient working of various cellular enzyme systems concerned in carbohydrate metabolism (Sumner and Somers 1947), no magnesium-deficiency syndrome has yet been recognised in association with diabetic ketosis. Calcium loss occurs during the development of this condition and continues during the treatment phase while the patient is confined to bed. When therapy is begun, slight reduction of the serum-calcium level has been reported (Martin and Wertman 1947). However, adequate reserves of calcium are usually available in the skeleton, and there is no evidence that additional calcium is required.

The cellular repair solution should therefore contain potassium, phosphate, and magnesium, with sodium and chloride to cover continuing urinary loss of these electrolytes. The following cellular repair solution ‡ is suggested. Its administration should be started when the blood-sugar level begins to fall, and it should be given at the rate of 1 litre every 4–6 hours:

Sodium chloride 1·17 g.
Dipotassium hydrogen phosphate 0·87 g.
Potassium chloride 1·49 g.
Magnesium chloride 0·24 g.
Glucose 50·0 g.
Distilled water to 1 litre

Sodium 20 m.eq. per litre
Potassium 30 m.eq. per litre
Chloride 45 m.eq. per litre
Phosphate 10 m.eq. per litre
Magnesium 5 m.eq. per litre
Glucose 5%

Intravenous administration of fluid should be discontinued as soon as possible, but it is wise to start to give fluids by mouth at least eight hours before this is done. If nausea persists gastric lavage may be helpful. If sips of water are well tolerated, drinks containing glucose and potassium should be given. A useful mixture contains glucose 50 g. dibasic potassium-phosphate 2 g. in 500 ml. of water flavoured with orange-juice. Up to 2 litres of this mixture (containing about 90 m.eq. of potassium and phosphate) should be given daily for two or more days, or until the patient is taking a full diet. These supplements of potassium have been shown to accelerate the restoration of cellular potassium (fig. 7) and to prevent the accumulation of excess sodium in the cells (fig. 6). Milk feeds may be tried next, and as soon as possible a high-carbohydrate 1000-calorie diet, and a rapid return to normal food. A high-protein intake is important because of the delay in achieving a positive nitrogen balance, but is poorly tolerated by patients recovering from diabetic ketosis. A positive nitrogen balance can be achieved at an early stage of treatment if a high-protein intake is maintained by continuous intragastric drip. An emaciated old lady, who developed severe ketosis after a long period of inadequately controlled diabetes, from the third to the fifth day after the start of treatment was given each day 2·4 litres of a fluid containing 201 g. of protein.§ Her condition improved rapidly; cell nitrogen balance was strongly positive (during the ten days 25 g. of nitrogen was restored to the cells): there was no significant rise in the plasma level of non-protein nitrogen (fig. 8).

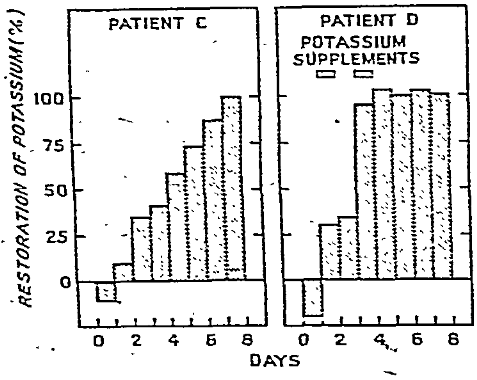

Fig. 7—Percentage restoration of potassium in treatment of diabetic ketosis. Patient D received 260 m.eq. of potassium in addition to the diet, and restoration was completed more rapidly than in patient C, who took only the diet (45 m.eq. per day).

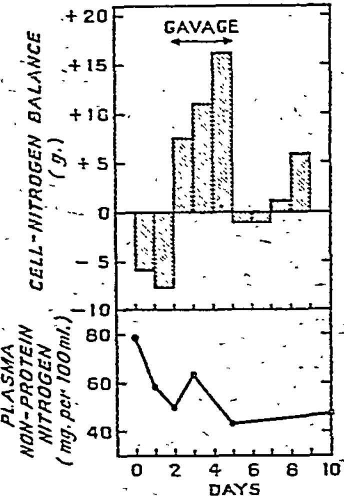

Fig. 8—Treatment of diabetic ketosis, showing daily balances of cell nitrogen and effect of large protein intake (201 g. daily) by continuous gavage.

MANAGEMENT OF SEVERE DIABETIC KETOSIS

We believe that, as Graham (1950) has clearly indicated, the treatment of severe diabetic ketosis should not be left to the house-physician. This is a grave medical emergency, especially in the elderly and in the presence of peripheral circulatory failure or severe infection. Treatment by an experienced team of doctors with facilities for rapid biochemical estimations can greatly reduce the mortality. A rigid therapeutic programme has no place in the treatment of this condition. The plan outlined here is intended as a guide to the application of the recommendations contained in the foregoing paragraphs in the management of severe ketosis.

As soon as the clinical diagnosis is made, 80 units of soluble insulin should be given intramuscularly and 20 units intravenously. Blood should be taken for the estimation of glucose; electrolyte and bicarbonate levels are useful but not essential. Treatment should on no account be delayed for the result of the tests. An intravenous infusion of the saline-lactate solution described above should be set up and allowed to run in rapidly. The result of the blood-sugar estimation should be available in 30–40 minutes: and, if it is over 600 mg. per 100 ml., a further 100 units of insulin should be given. If vomiting continues, gastric lavage may be done, but the stomach should be left empty. Blood-pressure should be measured every 30 minutes; and, if there is evidence of circulatory collapse, blood-transfusion is urgently indicated.

Blood-sugar estimation should be repeated 1½ hours after the insulin has been given. If the blood-sugar level is rising, double the previous dose of insulin should now be injected; if it is unchanged, the same dose should be repeated; but, if it is falling, insulin should be withheld. Insulin injections are given two-hourly until the blood-sugar level begins to fall. The size of the dose is regulated by blood-sugar estimations, and a fifth should be given intravenously and the remainder by intramuscular injection.

Intravenous therapy with the "saline-lactate" solution should be continued; one litre may be given in the first 15 minutes, the second litre in the next hour, and the third litre more slowly. When the blood-sugar level begins to fall, the "glucose electrolyte" or cellular repair solution may be substituted. One litre should be given every 4–6 hours. This solution must not be used unless there is a normal output of urine.

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‡ Butler (1950) states that autoclaving solutions containing magnesium and phosphate leads to the formation of a precipitate. This has been confirmed, but if the solution is allowed to stand for 24 hours it redissolves. Some caramelisation takes place in autoclaving this solution, but no untoward effects have followed administration. It can be prevented by adding 0·06% sodium metabisulphite to the solution, but this leads to a small increase in the sodium concentration.

§ The mixture contained glucose 120 g., dried skimmed milk 60 g., and calcium caseinate 120 g. in 2400 ml. of milk. Calorie value about 2600.

Urinary sugar tests are of no value in guiding insulin dosage while the blood-sugar level is above 300 mg. per 100 ml. Once it has fallen to this figure, specimens should be tested every three or four hours and insulin and glucose given accordingly. Repeated catheterisation is not usually necessary at any stage.

Nothing should be given by mouth until the blood-sugar level is approaching a normal figure. At this time, if the patient can swallow, sips of water may be tried. If this is well tolerated, potassium-containing drinks and milk may be offered and, as soon as possible, a full diet.

Diabetic ketosis is often precipitated by an infection; therefore any predisposing cause should be sought so that appropriate treatment may be instituted. The chest should be X-rayed, and the urine examined microscopically. In some cases an electrocardiogram may give evidence of an unsuspected coronary thrombosis. The prophylactic administration of antibiotics is indicated in all the cases. The intensive carbohydrate metabolism that follows treatment of diabetic ketosis requires considerable quantitites of the co-enzymes derived from the vitamin-B complex. Daily administration of a suitable parenteral preparation containing about 20 mg. of vitamin B_1, 80 mg. of nicotinamide, 8 mg. of riboflavine, 8 mg. of pyridoxine, and 12 mg. of pantothenic acid is therefore indicated.

ILLUSTRATIVE CASE-RECORDS

The following case-records indicate how these principles were applied in two patients.

Case 1 (fig. 1*a*).—A woman, aged 58, who had had diabetes for seven years, usually took 36 units of insulin a day. On Christmas Day, 1949, she went to Margate. She discovered on arrival that she had left her syringe at home, and for the next two days ate (and drank) well without taking insulin. She returned home on the 28th, thirsty, with polyuria and vomiting. Her husband gave her insulin on the 29th, but she continued to vomit and feel weak.

On admission to hospital on Dec. 30 very drowsy, irrational, dehydrated, and ketotic, with pulse-rate 120 and blood-pressure 58/40 mm. Hg. Insulin 160 units I.M. and 40 units I.V. was given at once, and 1·5 litres of saline-lactate solution given intravenously in an hour. When the blood-sugar level was reported to be 936 mg. per 100 ml. and carbon dioxide combining power 17 vols. per cent., a further 100 units of insulin was given. After an hour the blood-pressure was still 60/40 mm. Hg, and 200 ml. of double-strength plasma was given, the blood-pressure rose to 84/50 mm. Hg, and a further 1·5 litres of saline lactate was given. The blood-sugar level two hours after admission was 684 mg. per 100 ml., and, since it had fallen, no insulin was ordered; two hours later the level was 600 mg. per 100 ml. and a further 200 units of insulin was injected. At this stage the I.V. drip fluid was changed to the glucose-electrolyte solution, and 3 litres was given over the next twelve hours. The next two blood-sugar levels were 400 mg. per 100 ml. and 200 mg. per 100 ml., the ketosis cleared, the blood-pressure rose to 110/70 mm. Hg, and subsequent doses of insulin were controlled by urinary sugar tests.

Case 2.—A woman, aged 73, had had diabetes for fourteen months, and despite a history of a previous episode of ketosis requiring large amounts of insulin she had remained controlled for some months on diet alone. She had developed thirst and polyuria three weeks before admission, and had been restarted on insulin. Ten days later her diabetes suddenly became very difficult to control, and ketosis developed.

On admission she was drowsy but rational, dehydrated, ketotic, with blood-pressure 160/70 mm. Hg and pulse-rate 108. 100 units of insulin was given at once, partly I.V. and partly I.M., and an intravenous saline-lactate drip started. When the results of the initial biochemical investigations (blood-sugar 605 mg. per 100 ml., carbon dioxide combining power 9 vols. per cent.) were received, a further 100 units of insulin was given. Shortly after this, widespread urticaria developed, intravenous anti-histamine therapy was started, and an attempt was made at rapid desensitisation, all subsequent injections of insulin being given by the intramuscular route alone. Two hours later the blood-sugar level was 812 m
per 100 ml. and 300 units of insulin was given. The nex
blood-sugar level was 856 mg. per 100 ml. and 500 units o
insulin was injected, and the next blood-sugar level 844 m
per 100 ml. and 1000 units was given. After this the blo
sugar fell to 614 mg. per 100 ml. and insulin was omitted,
two hours later, since the blood-sugar level had risen to
mg. per 100 ml., another dose of 1000 units was inject
Subsequent blood-sugar levels and insulin doses are sho
in fig. 1*b*. The intravenous therapy was not changed
glucose-electrolyte solution when the blood-sugar level
initially, because the urinary output was unsatisfactor
a litre of 5% glucose in half-strength physiological sali
solution was given instead, and, when the fall of blood-su
level was arrested, further saline-lactate solution was use

SUMMARY

Although ketosis is a common and important co
plication of diabetes mellitus, its *treatment remai*
controversial. Rational therapy can only be founded
knowledge of the biochemical disturbances that have
be corrected.

Insulin should be started as soon as possible, and lar
doses used from the beginning. Rapid reduction of t
blood-sugar level is essential, and this can only be do
if insulin therapy is controlled by frequent estimatio
of the blood-sugar level.

Rapid replacement of extracellular fluid can
achieved by intravenous therapy with a "saline-lactate
solution. There is no definite evidence of the value
intensive alkali therapy, and it may lead to addition
metabolic disturbances.

Early administration of glucose leads to loss of wat
and electrolytes in the urine and is contra-indicated.
should only be given when the blood-sugar level falls.

Considerable losses of cellular water, electrolytes, a
nitrogen have been demonstrated. In untreated patien
plasma-potassium levels are often raised, and potassiu
containing solutions should not be given in the ear
stages. The levels *fall soon after the start of treatme*
with insulin and intravenous fluid, and then solutio
containing potassium and other cellular electrolyt
should be given. A suitable cellular repair solution
suggested, its administration may safely be started whe
the blood-sugar level begins to fall, and will *prevent t*
development of severe hypokalæmia. When the patien
can take fluids by mouth, supplements of potassiu
phosphate will accelerate restoration of cellular electro
lytes and prevent the accumulation of excess sodiu
in the cells.

We wish to thank Prof. M. L. Rosenheim for the great hel
he has given us in the preparation of this paper.

REFERENCES

Atchley, D. W., Loeb, R. F., Richards, D. W. jun., Benedict, E. M
Driscoll, M. E. (1933) *J. clin. Invest.* 12, 297.
Bollet, S., Steiger, W. A., Nadler, C. S., Gazes, P. C. (1950) *Am*
J. med. Sci. 219, 512.
Black, A. B., Malins, J. M. (1949) *Lancet*, i, 56.
Bruch, E. (1950) *Arch. intern. Med.* 86, 427.
Bruger, M., Friedman, B. (1938) *Proc. Soc. exp. Biol., N.Y.* 38, 8
Buchanan, J. M., Hastings, A. B., Nesbett, F. B. (1949) *J. bio*
Chem. 180, 435.
Butler, A. M. (1950) *New Engl. J. Med.* 243, 618.
— Talbot, N. B., Burnett, C. H., Stanbury, J. B., Maclachla
E. A. (1947) *Trans. Ass. Amer. Phys.* 60, 102.
Collen, M. F. (1942) *Arch. intern. Med.* 70, 317.
Danowski, T. S., Winkler, A. W., Peters, J. P. (1946) *Yale J. Bio*
Med. 18, 405.
— Peters, J. H., Rathbun, J. C., Quashnock, J. M., Greenma
L. (1949) *J. clin. Invest.* 28, 1.
Darrow, D. C., Pratt, E. L. (1950) *J. Amer. med. Ass.* 143, 365.
Eliel, L. P., Pearson, O. H., Rawson, R. W. (1950) *New Engl. J*
Med. 243, 471.
Finch, C. A., Marchand, J. F. (1943) *Amer. J. med. Sci.* 206, 60
— Sawyer, C. G., Flynn, J. M. (1946) *Amer. J. Med.* 1, 337.
Franks, M., Berris, R. F., Kaplan, N. O., Myers, G. B. (1947) *Arc*
intern. Med. 80, 739.
Frenkel, M., Groen, J., Willebrands, A. F. (1947) *Ibid*, p. 728.
Graham, G. (1950) *J. R. Inst. publ. Hlth*, 13, 263.
Greenman, L., Mateer, F. M., Gow, R. C., Peters, J. H., Danow
T. S. (1949) *J. clin. Invest.* 28, 409.
Guest, G. M. (1949) *Amer. J. Med.* 7, 630.
Haldane, J. B. S., Wigglesworth, V. B., Woodrow, C. E. (19
Proc. roy. Soc. B, 96, 15.

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POSTURAL NERVE BLOCK FOR INTRANASAL OPERATIONS

E. S. CURTISS
M.B. Lond., D.A.

CONSULTANT ANÆSTHETIST, MILLER GENERAL HOSPITAL, GREENWICH, AND KING EDWARD MEMORIAL HOSPITAL, EALING

IN 1941 A. J. Moffett first described a new method of obtaining local analgesia for intranasal surgery Moffett 1941, 1944, 1947). The analgesic solution* is nstilled into the nostrils and is distributed by placing the head in suitable positions. Three different positions are used and one third of the total volume of analgesic solution is instilled into the nostrils in each of them. Ten minutes is allowed in each position for analgesia to develop, making an over-all time of thirty minutes to complete the analgesia.

My attention was drawn to this method when one of my surgical colleagues asked me to use it. I did so and soon found the analgesia thus induced far superior to, and more reliable than, that obtained with the old technique of applying cocaine by ribbon-gauze packing, painting, or spraying. Where there is a nasal deformity the solution can penetrate to areas not reached by packing. Also the method avoids trauma and is much less uncomfortable for the patient.

I used Moffett's original technique in over 150 patients and felt convinced of its superiority. Indeed the analgesia was so complete that it seemed to be the result of a nerve block. Simple contact between solution and mucosa could not, I concluded, have such widespread effects.

ANATOMY OF THE REGION

In order to find exactly where the solution was deposited I repeated Moffett's technique on 6 volunteer patients using an aqueous solution of radio-opaque dye. Radiographs showed that in each of the three positions the bulk of the solution accumulated in a small pool just under the roof of the nose. In the two lateral positions a trace of solution lay underneath the inferior turbinate bones each side. There was no trace of dye anywhere else.

This suggested that the analgesia was produced by the accumulation of the solution in the region of the spheno-ethmoidal recess on each side, where it would affect the sphenopalatine ganglion and its branches (fig. 1). The sensory nerve-supply of the nasal cavity is largely derived through this ganglion. The three areas not supplied are:

Ethmoidal and infundibular regions, supplied by the anterior ethmoidal nerve from the ophthalmic division of the 5th cranial nerve. In fact the anterior ethmoidal nerve *is* blocked, as its point of entry into the nasal cavity lies in the area occupied by the pool of analgesic solution.

Columella and vestibule (anterior to mucocutaneous junction), supplied by the terminal branch of the ophthalmic division of the 5th. Moffett deals with this deficiency by injecting a little 1% procaine solution into the columnella. From the practical point of view this is necessary *only if* the surgeon wishes to make his initial incision anterior to the mucocutaneous junction when performing a submucous resection. An incision posterior to the mucocutaneous junction obviates the need for this injection.

Anterior part of inferior lateral wall and septum, supplied by the anterior and posterior superior dental nerves from the maxillary division of the 5th. This area is usually analgesic too, for reasons given later.

DEVELOPMENT OF NEW METHOD

These observations suggested that the success of the method depended on placing a sufficiently large pool of analgesic solution in the superior meatus of the nose on each side.

The chief drawbacks to Moffett's technique are the length of time required to complete analgesia (thirty minutes) and the need for the anæsthetist to change the patient's position three times to make three separate instillations. I thought that if the analgesic solution could be placed in the superior meatus on each side in one manœuvre, these drawbacks could be overcome. Analgesia might be obtained with a single instillation and the time required to prepare the patient for operation might be cut by some twenty minutes.

Moffett's second position seemed the obvious one to try. After instillation of analgesic solution into the nose on each side, the patient is asked to pinch his nostrils with his finger and thumb and is helped to roll over on to his face with his head well flexed over the end of the table or trolley. I found, however, that using this position alone, leakage of solution from the nose often resulted in inadequate analgesia.

Further trial and error led to the development of a technique which has now proved satisfactory and reliable in over 200 cases.

TECHNIQUE

4 ml. of the analgesic solution already described is drawn into a 5 ml. syringe attached to a special needle 2 in. long, blunt-ended and perforated with three lateral holes near its end. This needle is bent in the middle to an angle of 45° (fig. 2). The patient lies on his back with his shoulders supported on a pillow and his head fully extended over the end of the trolley or table (fig. 3). The needle is inserted with the tip directed along the floor of the nose. When the angle of the needle enters the nose the direction of the tip is altered to point towards the roof of the nose. When the tip impinges on the bony

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* Cocaine hydrochloride (8%) 2 ml.;
Sodium bicarbonate solution (1%) 2 ml.;
Adrenaline hydrochloride solution (1 : 1000) 1 ml.

DR. NABARRO AND OTHERS: REFERENCES—*continued*

Harvey, A. M. (1948) *Proc. Inst. Med., Chicago*, 17, 182.
Harwood, R. (1951) *New Engl. J. Med.* 245, 1.
Himsworth, H. P. (1932) *Lancet*, ii, 165.
— (1949) *Brit. med. J.* i, 632.
Holler, J. W. (1946) *J. Amer. med. Ass.* 131, 1186.
Joslin, E. P. (1946) The Treatment of Diabetes Mellitus. 8th ed., London.
Kety, S. S., Polis, B. D., Nadler, C. S., Schmidt, C. F. (1948) *J. clin. Invest.* 27, 500.
Kjerulf-Jensen, K., Krarup, N. B., Warming-Larsen, A. (1951) *Lancet*, i, 372.
Lange, K., Graig, F., Tchertkoff, V., Oberman, J., LoCasto, F. (1951) *Amer. J. med. Sci.* 222, 61.
Lardy, H. A., Ziegler, J. A. (1945) *J. biol. Chem.* 159, 343.
Lawrence, R. D. (1949) *Lancet*, i, 123.
Lipsett, M. N., Crescitelli, F. (1950) *Arch. Biochem.* 28, 329.
Logsdon, C. S., McGavack, T. H. (1948) *J. clin. Endocrinol.* 8, 658.
McCance, R. A., Lawrence, R. D. (1935) *Quart. J. Med.* 4, 53.
Mackler, B., Lichtenstein, H., Guest, G. M. (1951) *Amer. J. Physiol.* 166, 191.
Martin, H. E., Wertman, M. (1947) *J. clin. Invest.* 26, 217.
— — Westover, L., Simonsen, D. G., Mehl, J. W. (1950) *Calif. Med.* 72, 133.
Mirsky, I. A., Heiman, J. D., Broh-Kahn, R. H. (1937) *Amer. J. Physiol.* 118, 290.
— Franzblau, A. N., Nelson, N., Nelson, W. E. (1941) *J. clin. Endocrinol.* 1, 307.
— Podore, C. J., Wachman, J., Broh-Kahn, R. H. (1948) *J. clin. Invest.* 27, 515.
Nabarro, J. D. N., Spencer, A. G., Stowers, J. M. (1952) *Quart. J. Med.* 21, 225.
Nadler, C. S., Bellet, S., Gazes, P. C., Steiger, W. A. (1950) *J. Lab. clin. Med.* 35, 842.
Neubauer, R. A., Frelick, R. W. (1950) *Amer. Heart J.* 40, 793.
Nicholson, W. M., Branning, W. S. (1947) *J. Amer. med. Ass.* 134, 1292.
— Spaeth, W. (1949) *South. med. J.* 42, 77.
Oakley, W. (1949) *Brit. med. J.* i, 724.
Peters, J. P. (1945) *Yale J. Biol. Med.* 17, 705.
— (1946) *Amer. J. digest. Dis.* 13, 127.
Root, H. F. (1945) *J. Amer. med. Ass.* 127, 557.
— Carpenter, T. M. (1943) *Amer. J. med. Sci.* 206, 234.
Seldin, D. W., Tarail, R. (1950) *J. clin. Invest.* 29, 552.
Soskin, S., Levine, R. (1937) *Amer. J. Physiol.* 120, 761.
— — (1944) *Amer. J. digest. Dis.* 11, 305.
— — (1946) Carbohydrate Metabolism. Chicago.
Spencer, A. G. (1950) *Lancet*, ii, 623.
Stephens, F. I. (1949) *Ann. intern. Med.* 30, 1272.
Sumner, J. B., Somers, G. F. (1947) Chemistry and Methods of Enzymes. New York.
Thorn, G. W., Forsham, P. H. (1950) *In* Williams, R. H., Textbook of Endocrinology. London.
Tuynman, P. E., Wilhelm, S. K. (1948) *Ann. intern. Med.* 29, 856.
Webster, D. R., Henrikson, H. W., Currie, D. J. (1950) *Ann. Surg.* 132, 779.
Wierzuchowski, M. (1936) *J. Physiol.* 87, 311.
— (1937) *Ibid*, 90, 440.

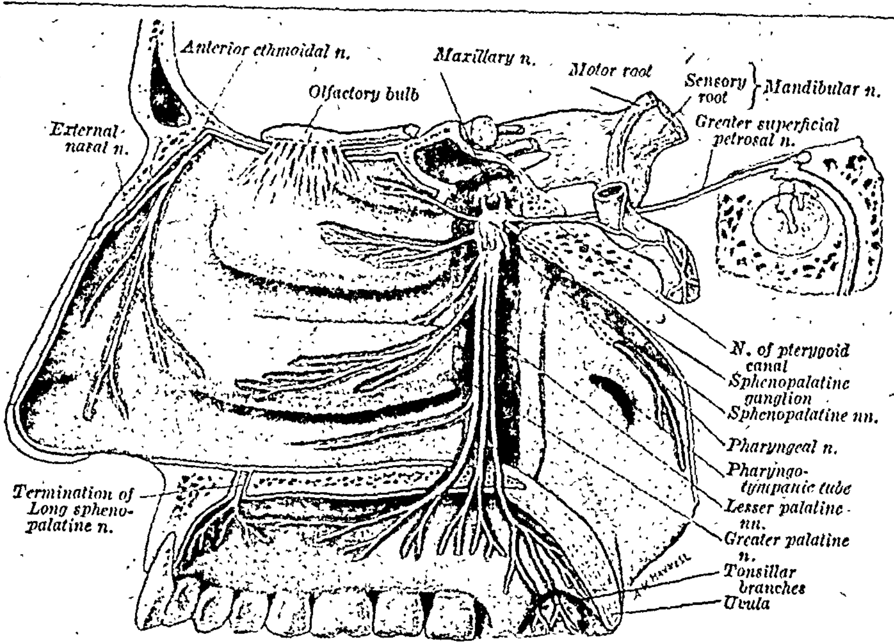


Fig. 1—The right sphenopalatine ganglion and its branches. Semi-diagrammatic. (Fig. 950 in the 30th edition of *Gray's Anatomy* reproduced by courtesy of the Editor.)

roof 2 ml. of solution is run in and the syringe is withdrawn. The procedure is then repeated in the other nostril.

The patient remains in this position for ten minutes, by which time analgesia will be complete. It is important that he should be told not to lift or move his head during this time, and I have found it useful to have the attending nurse or orderly sit on a stool at the patient's head to support the head, or at least to see that no undue movement occurs. At the end of the ten minutes the patient is allowed to wriggle back into a more comfortable position on the trolley. Before moving, he is told to hold any excess solution displaced into his pharynx or mouth and given a bowl to expectorate into if necessary. A few patients have swallowed the excess solution, but I have yet to see any ill effects from this.

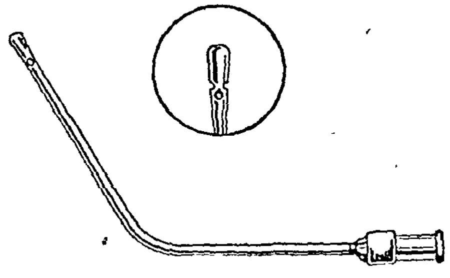


Fig. 2—Needle used to instil analgesic solution.

DISCUSSION

Radiographs with radio-opaque solution show a pool of fluid deposited in the superior meatus in such a way that it is certain to affect the sphenopalatine ganglion and its branches in the nose, and the anterior ethmoidal nerve where it enters the nasal cavity (fig. 4). The main trunk of the maxillary division of the 5th cranial nerve crosses the sphenomaxillary fossa nearby and is always affected to some degree, as is shown by the fact that the area immediately beneath the inferior turbinate bones, supplied by the anterior and posterior superior dental nerves, is analgesic. Sometimes the lateral wall and floor of the antrum are also analgesic.

The latter observation has made it possible to extend the advantages of local analgesia by this method to most intranasal surgery, including the Caldwell-Luc operation. In one or two cases where analgesia of the antrum has not been complete, the remaining 1 ml. of solution has

necessary in these cases also to infiltrate the alveolar-buccal mucosa, with 1% solution of procaine.

Hæmostasis is excellent and it has been suggested that the analgesic solution, by nerve blockage, produces a collar constriction of the arterial supply as it enters the nasal cavity, together with an increase of venous drainage.

The degree of penetration of the main trunk of the 5th nerve depends partly on the thickness of the mucous membrane (which varies from person to person and with pathological processes) and partly on the size of the pool of analgesic solution.

Though the superior part of the pharynx is analgesic—which enables posterior polypi projecting into the nasopharynx to be dealt with—the inferior part is not. There is no interference with the ability to swallow, nor is there danger of accidentally inhaling blood or pus during or after operation for the laryngeal reflexes are not affected.

The absence of trauma in this technique may, I think, largely explain the absence to date of any untoward symptoms attributable to cocaine; if there are no raw surfaces, cocaine is less likely to be absorbed into the circulation in a quantity sufficient to produce toxic symptoms. Moreover, the amount of cocaine used (approximately 2 grains) is well below the minimal lethal dose for topical application.

Two or three of my younger patients (adolescents) have been quite euphoric; but this has been no disadvantage, as they have kept themselves and the theatre staff entertained during the operation! I have, however, recently reduced the total volume of analgesic solution in my younger and smaller patients—the reduction being based on a fractional proportion of 10 stone.

In conclusion I would like to emphasise the advantages of intranasal operations under local rather than general anæsthesia. The hæmostasis it affords gives the surgeon a clearer view of his field and allows the operation to be performed much more rapidly. Loss of blood is negligible, and the patient is conscious and coöperative. The postoperative sore throat which so often follows the packing of the throat required with general anæsthesia is also avoided; and there is no danger of postoperative inhalation of blood or pus.

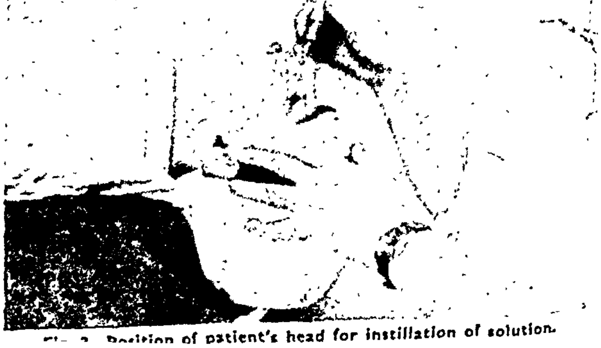


Fig. 3—Position of patient's head for instillation of solution.

SUMMARY

A simple, reliable method of postural nasal block is described.

Local analgesia for most intranasal operations can be obtained by instilling analgesic solution into the nostrils and then keeping the head, for ten minutes in such a position that the solution forms a pool in the region of the spheno-ethmoidal recess.

In this situation the analgesic blocks the sphenopalatine ganglion and its branches, which are largely responsible for the sensory supply to the nasal cavity. Branches of the 5th cranial nerve passing near the pool of solution are also usually affected.

Results are so satisfactory alike to the patient, the surgeon, and the anæsthetist. It is hoped that this method will be more widely used.

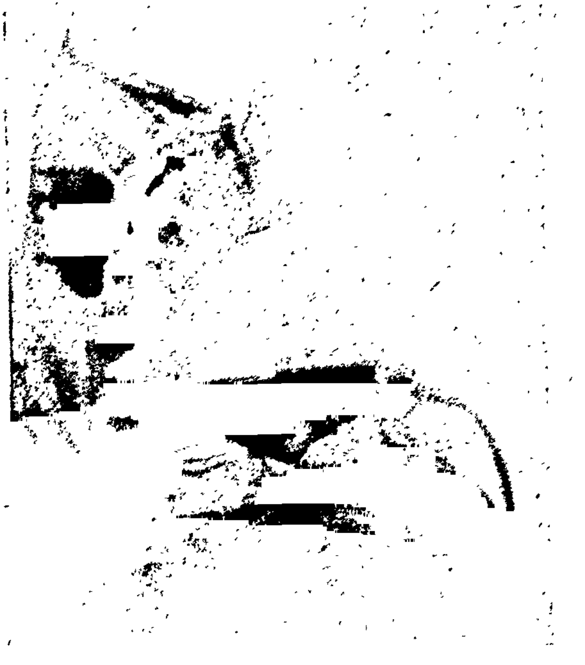


Fig. 4—Radiograph showing pool of radio-opaque solution in the superior meatus.

My thanks are due to my colleagues: to Mr. J. W. S. H. Lindahl, who first drew my attention to Moffett's work and asked me to use his method, and to Mr. E. Gwynne Evans, who has given me every encouragement in the investigations leading to this modification of Moffett's method. Also to Mr. Moffett himself, who has shown a personal interest in this work. I am grateful, too, for the helpful coöperation of Prof. J. Whillis, of Guy's Hospital, and members of the radiological department at the Miller General Hospital, and of others who have assisted in various ways.

REFERENCES

Moffett, A. J. (1941) *J. Laryng.* 56, 429.
— (1944) *Ibid*, 59, 151.
— (1947) *Anæsthesia*, 2, 31.

"... The need to make attendance at lectures compulsory should be regarded as a sign of grave disease in the teaching system, especially since students can read all that they are obliged to know, and lectures are intended to lighten the task of selection. Where the lecturer fails to carry out his duties efficiently, a student should have the right to indicate this by the mute protest of his absence, though a more vocal complaint would obviously be preferable. Compulsory lectures, it has been well said, maintain both bad students and bad lecturers."—Dr. A. G. OETTLÉ, *S. Afr. med. J.* 1952, 26, 240.

MONOHYDROXYBENZOIC ACIDS AND ASCORBIC ACID DEPLETION OF THE ADRENAL GLANDS IN THE INTACT RAT

M. J. H. SMITH
M.Pharm.Wales, Ph.D. Lond., F.R.I.C.
LECTURER IN CHEMICAL PATHOLOGY, KING'S COLLEGE HOSPITAL MEDICAL SCHOOL, LONDON

Cochran et al. (1950) suggested that the mode of action of salicylates and cortisone was basically the same, because their clinical and metabolic effects in rheumatic fever were similar. This suggestion is supported by:

1. The development of a mild Cushing's syndrome in a patient with rheumatic fever treated with aspirin (Cochran et al. 1950).
2. The increased excretion of reducing steroids in patients receiving aspirin therapy (Van Cauwenberge and Heugshem 1951).
3. Significant depression in the number of circulating eosinophils by salicylates in man (Kelemen et al. 1950, Roskam et al. 1951).

It has been reported that salicylates cause eosinopenia and increased excretion of urinary 17-ketosteroids in guineapigs (Bertolani et al. 1951); a depletion of cholesterol in the adrenal cortex of rats (Robinson 1951, Van Cauwenberge 1951a); and a significant reduction of ascorbic acid in the adrenal glands of the intact rat (Blanchard et al. 1950, Pasqualini et al. 1950, Hetzel and Hine 1951, Van Cauwenberge 1951a). The amount of ascorbic acid in the adrenal glands is a measure of their cortical activity and is under the control of pituitary adrenocorticotrophic hormone (Sayers et al. 1946). The response to salicylates was not obtained in hypophysectomised animals, and it was concluded that salicylates exerted their effect on the adrenals indirectly through the pituitary. Hetzel and Hine (1951), on the basis of this evidence, held that the therapeutic effects of salicylates are mediated by the pituitary and adrenal glands.

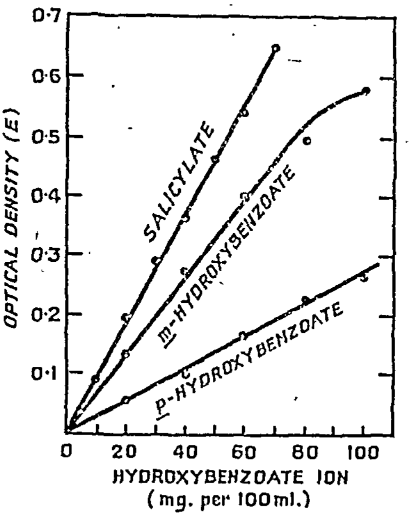
The specificity of this action of salicylates, or of compounds containing the characteristic salicyl grouping—e.g., *p*-aminosalicylic acid and 2-phenyl-3-hydroxycinchoninic acid—on the amount of ascorbic acid in the adrenals of the intact rat is open to question, because amidopyrine, acetanilide (Blanchard et al. 1950), and sodium benzoate (Van Cauwenberge 1951b) have been found to do the same. It seemed desirable, therefore, to find out what action on the ascorbic acid content of the adrenal gland would be exerted by the isomers of salicylic acid, *meta-* and *para-*hydroxybenzoic acids, which have no therapeutic activity in rheumatic fever (Stockman 1913).

METHODS

Animals.—Male rats of the Wistar strain weighing 215–305 g. were used throughout the experiment. In any one group the weights did not vary more than 50 g. The rats were housed in a warm room with the temperature controlled at 70° ± 1°F and maintained on a diet of Thompson rat cubes. Food was withheld during each experiment, and the injections were given intraperitoneally. Two hours after the injection (except for *p*-hydroxybenzoic acid, where extra intervals of half and one hour were used) the rats were deeply anæsthetised by the intraperitoneal injection of 1 ml. of a 10% solution of thiopentone. Both adrenal glands were removed through a single ventral incision, cleaned of fat, weighed, and prepared for analysis by the method of Sayers et al. (1948). Blood for the estimation of the hydroxybenzoate levels was taken from the inferior vena cava into oxalated tubes after excision of the adrenal glands.

Injections.—All the substances were given as 10% solutions of their sodium salts in sterile water. The pH values of the solutions, measured with 'Universal' indicator papers (B.D.H.), were between 6·7 and 7·0 units. One group of rats received no injection, and three groups were injected with 1 ml. of physiological saline solution. The dosage of salicylates was based on the amount found by Blanchard et al. (1950) to produce a good response in the rat, and approximately equivalent amounts of the other substances were used.

Estimations.—The amount of ascorbic acid in the adrenal glands was estimated by the method of Roe and Kuether (1943), the result being expressed as mg. per 100 g. of fresh adrenal tissue. The plasma-salicylate levels were measured by the method of Smith and Talbot (1950), and the plasma level of the *m*- and *p*-hydroxybenzoates were determined by the same method (see figure). Twelve control estimations were made on plasma from untreated rats, and a mean figure equivalent to 7·6 mg. per 100 ml. of salicylate ion was obtained. This level was taken as zero, and all the figures for rats treated with salicylate were expressed relative to this zero in mg. per 100 ml.; zero corrections for the other two acids were applied to the appropriate estimations.



Calibration curves for salicylate, *m*-hydroxybenzoate, and *p*-hydroxybenzoate in distilled water.

RESULTS

Sodium Salicylate, Sodium m-*Hydroxybenzoate, and Sodium Benzoate*

The effects of these substances on the amount of ascorbic acid in the adrenal glands of intact rats was compared with the effect of physiological saline solution. To control the effect of handling and injection, a group of rats which had received no injection was compared with the saline-treated rats. The results are shown in table I together with the plasma levels of salicylate and *m*-hydroxybenzoate.

These results show that, compared with saline solution, the three substances significantly deplete the ascorbic acid of the adrenal glands in intact rats. No significant difference between the untreated rats and those treated with saline was observed. A significant difference exists between the groups treated with salicylate and with *m*-hydroxybenzoate ($P < 0·001$), but the difference between the plasma levels of these two substances probably explains this. A significant difference ($P < 0·01$) exists between the groups treated with salicylate and with benzoate, but plasma-benzoate levels could not be estimated.

Sodium p-*Hydroxybenzoate*

Blanchard et al. (1950) reported that *p*-hydroxybenzoic acid did not significantly deplete the ascorbic acid in the adrenal glands when these were removed two hours after injection of the acid. *p*-Hydroxybenzoic acid is rapidly converted into the readily excreted *p*-hydroxyhippuric acid, and caused increased urinary excretion of uric acid when collections were made for only a few hours after the ingestion of the substance. When twenty-four-hour specimens of urine were used, no such effect could be demonstrated, though salicylates showed a pronounced activity (Quick 1932). This evidence suggested that the two-hour interval between injection and removal of the adrenals may have been too long. Three groups of rats were therefore used, the intervals between administration of the *p*-hydroxybenzoate and excision of the adrenal glands being half an hour, one hour, and two hours. Groups of rats treated with physiological saline solution, with the same time intervals between injection and removal of adrenals, were used as controls. The results are shown in table II together with the plasma levels of *p*-hydroxybenzoate.

It will be seen that *p*-hydroxybenzoic acid significantly depleted the adrenal ascorbic acid half an hour and one hour after injection, but no such response was

TABLE I—EFFECT OF SODIUM SALICYLATE, SODIUM *m*-HYDROXYBENZOATE, AND SODIUM BENZOATE ON AMOUNT OF ASCORBIC ACID IN ADRENAL GLANDS OF RATS

Group no.	Injection	No. of rats	Mean ascorbic acid (mg. per 100 g. of wet adrenal) 2 hr. after injection	Mean plasma-hydroxybenzoate level (mg. per 100 ml.)
1	None	8	411 ± 35·0 (362–473)	—
2	[illegible] saline solution 1 ml.	7	386 ± 12·0 (345–454)	—
3	[illegible] per kg. of body-weight	8	130 ± 15·3 (115–158)	52·0 ± 7·6 (42·5–67·5)
4	[illegible] 330 mg. per kg. of body-weight	6	292 ± 19·9 (280–332)	16·25 ± 4·5 (11·5–22·0)
5	[illegible] per kg. of body-weight	8	183 ± 29·9 (147–223)	—

Comparison of the ascorbic acid results:
For Groups 1 and 2: n = 13, t = 1·3321, P = 0·3
Groups 2 and 3: n = 13, t = 17·6416, P = 0·001
Groups 2 and 4: n = 11, t = 6·0743, P = 0·001
Groups 2 and 5: n = 13, t = 11·6215, P = 0·001

All means in tables I and II are given with their standard deviations and ranges.

TABLE II—EFFECT OF SODIUM *p*-HYDROXYBENZOATE ON AMOUNT OF ASCORBIC ACID IN ADRENAL GLANDS OF RATS

Group no.	Injection	No. of rats	Interval between injection and removal of adrenals (hr.)	Mean ascorbic acid (mg. per 100 g. of wet adrenal)	Mean plasma-*p*-hydroxybenzoate (mg. per 100 ml.)
6	Physiological saline solution 1 ml.	7	1/2	379 ± 16·0 (357–410)	—
7	Sodium *p*-hydroxybenzoate 400 mg. per kg. of body-weight	8	1/2	303 ± 20·6 (275–329)	20·0 ± 6·2 (21·5–36·5)
8	Physiological saline solution 1 ml.	7	1	396 ± 14·3 (381–415)	—
9	Sodium *p*-hydroxybenzoate 400 mg. per kg. of body-weight	6	1	332·5 ± 28·2 (295–363)	8·1 (0–22·0)
10	Physiological saline solution 1 ml.	7	2	386 ± 37·8 (315–454)	—
11	Sodium *p*-hydroxybenzoate 400 mg. per kg. of body-weight	5	2	346 ± 27·0 (313–371)	0

Comparison of ascorbic acid results:
For Groups 6 and 7: n = 13, t = 7·7143, P = 0·001
Groups 8 and 9: n = 11, t = 6·8065, P = 0·001

observed after two hours. The results from the untreated rats, group 1 of table I, did not differ significantly from those of the rats treated with saline solution at half an hour, one hour, and two hours ($P > 0{\cdot}2$).

Summary of Results

The sodium salts of the three isomeric monohydroxybenzoic acids and sodium benzoate significantly reduce the amount of ascorbic acid in the adrenal glands of the intact rat. The degree of change in the ascorbic acid content of the adrenals corresponds approximately to the concentration of the hydroxybenzoates in the plasma at the time when the glands are excised. Salicylate produces the highest plasma level and the largest depletion of adrenal ascorbic acid two hours after injection. *p*-Hydroxybenzoate gives its highest plasma level and largest depletion of adrenal ascorbic acid half an hour after injection and cannot be detected in the blood one and a half hours later, when no significant change in adrenal ascorbic acid is observed.

DISCUSSION

If salicylates act through the pituitary and adrenal glands, they may do so in three ways:

(1) By blocking the destruction of adrenal corticoids, or by increasing tissue sensitivity to them, they may reinforce the action of the natural hormones.

(2) They have an adrenocorticotrophic action.

(3) They may stimulate the pituitary and thereby the adrenals.

If the first explanation is correct, salicylates and adrenal corticoids (of which cortisone may be considered a typical example) should have the same general effects on the tissues. But in some respects the action of salicylates seems to be opposed to that of cortisone (Meade and Smith 1951b). In particular, salicylates cause a lessening of the glycosuria in rats made diabetic either by partial pancreatectomy (Ingle 1950) or alloxan (Bornstein et al. 1952), whereas cortisone exacerbated the diabetes in such rats.

Against the suggestion that salicylates have an adrenocorticotrophic action is the fact that they do not significantly reduce the amount of ascorbic acid in the adrenals of hypophysectomised rats (Van Cauwenberge 1951a).

There remains the third possibility—that salicylates indirectly stimulate the adrenals through the pituitary. Hetzel and Hine (1951) observed a reduction in the ascorbic acid of the adrenals of intact rats in which the plasma-salicylate was kept at a level found adequate in clinical medicine, and they concluded that the therapeutic effects of salicylates are mediated through the pituitary and adrenal glands. The present work demonstrates that this depletion of adrenal ascorbic acid in the intact rat is not specific to salicylates and is elicited by *m*- and *p*-hydroxybenzoates. Neither of these substances have any therapeutic activity in rheumatic fever, and therefore no relation exists between depletion of adrenal ascorbic acid in intact rats and the mode of action of salicylates in rheumatic fever. The same lack of specificity probably also applies to the depletion of cholesterol in the adrenal cortex of rats (Robinson 1951) and to the eosinopenia and increased excretion of 17-ketosteroids in guineapigs (Bertolani et al. 1951).

The reduction in the number of circulating eosinophils reported to occur in man four hours after the oral administration of salicylates (Kelemen et al. 1950) has not been confirmed by Meade and Smith (1951a) and Roskam et al. (1951). The latter workers observed an eosinopenia six hours after salicylates were given, but their eosinophil-counts were made on blood taken in the morning. It has recently been emphasised that the morning is an unsuitable time for measuring induced falls in eosinophils, because "spontaneous" decreases may be as large as 50% (Swanson et al. 1952). The development of features suggesting Cushing's syndrome in the patient of Cochran et al. (1950), and the gradual disappearance of these side-effects when the dose of aspirin was reduced, are difficult to explain. As an alternative to the contention that aspirin and cortisone have a common action, it has been suggested that a large endogenous production of adrenal corticoids is part of the patient's reaction to the rheumatic fever (*British Medical Journal* 1950).

SUMMARY

The effect of sodium *m*-hydroxybenzoate and of sodium *p*-hydroxybenzoate on the amount of ascorbic acid in the adrenal glands of the intact rat has been investigated.

Neither of these substances has any therapeutic activity in rheumatic fever, but they both deplete the adrenal ascorbic acid.

The significance of this finding is discussed with reference to the theory that the therapeutic action of salicylates is mediated by the pituitary and adrenal glands.

I wish to express my thanks to Miss E. Quilley and Miss M. Sandiford for able technical assistance, and to the Board of Governors of King's College Hospital for a grant towards the cost of the work.

REFERENCES

Bertolani, F., Lorenzini, R., Bonati, B. (1951) *Lancet*, i, 54.
Blanchard, K. C., Dearborn, E. H., Maren, T. H., Marshall, E. K. jun. (1950) *Bull. Johns Hopk. Hosp.* 86, 83.
Bornstein, J., Meade, B. W., Smith, M. J. H. (1952) *Nature, Lond.* 169, 115.
British Medical Journal (1950) ii, 1432.
Cochran, J. B., Watson, R. D., Reid, J. (1950) *Brit. med. J.* ii, 1411.
Hetzel, B. S., Hine, D. C. (1951) *Lancet*, ii, 94.
Ingle, D. J. (1950) *Proc. Soc. exp. Biol., N.Y.* 75, 673.
Kelemen, E., Majoros, M., Ivanyi, J., Kovacs, K. (1950) *Experientia*, 6, 435.
Meade, B. W., Smith, M. J. H. (1951a) *Lancet*, i, 773.
— — (1951b) *Ibid*, ii, 224.
Pasqualini, R. Q., Dosne de Pasqualini, C., Garberi, J. C. (1950) *Rev. Soc. argent. Biol.* 26, 120.
Quick, A. J. (1932) *J. biol. Chem.* 98, 157.
Robinson, F. B. (1951) *Brit. med. J.* i, 300.
Roe, J. H., Kuether, C. A. (1943) *J. biol Chem.* 147, 399.
Roskam, J., Van Cauwenberge, H., Mutsers, A. (1951) *Lancet*, ii, 375.
Sayers, G., Sayers, M. A., Liang, T. Y., Long, C. N. H. (1946) *Endocrinology*, 38, 1.
Sayers, M. A., Sayers, G., Woodbury, L. A. (1948) *Ibid*, 42, 379.
Smith, M. J. H., Talbot, J. M. (1950) *Brit. J. exp. Path.* 31, 65.
Stockman, R. (1913) *Brit. med. J.* i, 597.
Swanson, J. N., Bauer, W., Ropes, M. (1952) *Lancet*, i, 129.
Van Cauwenberge, H. (1951a) *Ibid*, ii, 374.
— (1951b) *Ibid*, p. 686.
— Heugshem, C. (1951) *Ibid*, i, 771.

HEXAMETHONIUM COMPOUNDS IN THE TREATMENT OF HYPERTENSION

J. D. BLAINEY
M.D. Lond., M.R.C.P.
MEDICAL REGISTRAR, QUEEN ELIZABETH HOSPITAL, BIRMINGHAM

THE appraisal of new therapeutic substances in hypertension is difficult, for its ætiology is unknown, and each patient shows striking and unpredictable variations in blood-pressure even without treatment. It is necessary to define certain blood-pressure levels in hypertensive patients before the effects of any treatment can be assessed, and four such levels may be recognised:

(1) *The consultation blood-pressure* is that obtained in the outpatient clinic or consulting-room. This reading is often considerably higher than that usually found by the patient's own practitioner.

(2) *The admission or resting blood-pressure* is found immediately after admission to hospital or following a period of quiet rest in the outpatient clinic.

(3) *The basal blood-pressure* is the lowest pressure found after several days, or occasionally weeks, in hospital, when the pressures are recorded by the same observer in the morning, before the patient rises, under strictly comparable conditions.

(4) *The narcotic blood-pressure* is the lowest reading obtained with sodium amylobarbitone ('Amytal') sedation or during natural sleep.

In the present series of 34 patients with hypertension an attempt has been made to assess these variations in each patient before treatment, and so to standardise the conditions of study as to minimise them in the interpretation of the results. All the blood-pressure readings were taken by auscultation in the same arm with a mercury sphygmomanometer. Systolic pressure was recorded as the point of first appearance of sounds as the pressure in the cuff is lowered, and the diastolic as the point of disappearance of the sounds, which has been shown to be closer to diastolic pressure measured directly by arterial puncture (Steele 1942).

CLINICAL MATERIAL

The hypertension was sufficiently severe in all the patients to warrant reference to consulting physicians either because of symptoms or because of the height of the blood-pressure. The cases form a selected group of severe hypertensives, and include several who were seriously ill with secondary cardiac or renal insufficiency; no cases of primary renal disease have been included. Seven further patients were studied in detail, but were not included in the trial, because their blood-pressures returned to normal values in hospital without treatment.*

ROUTINE OF STUDY

On the day of admission all the patients were fully examined and had their blood-pressure measured in recumbent, sitting, and standing positions. They were confined to bed, except for toilet purposes, for ten days and were then allowed up during afternoon and evening for a further five days before any treatment was started. In a few cases the observation period extended over three or four weeks. During this period detailed study was made of the variability of the blood-pressure. The effects of amylobarbitone sedation (Cady et al. 1936), immersion of the hand in cold water (Hines and Brown 1932), and exercise on the blood-pressure were observed. The pressure recorded in the morning, before the patient rose, was regarded as basal pressure for the day, because this was usually the lowest recorded during waking hours. During the period in hospital, both before and after treatment, the blood-pressure was always taken at this time on alternate days, six consecutive readings at thirty-second intervals being recorded, at first with the patient recumbent and then in the erect position. The lowest of these readings was noted as the basal blood-pressure for the day, and the average of the three basal readings as the basal pressure for the week. This gives a comparable figure for analysis before and after treatment, although it does not indicate the wide fluctuations of pressure that were usually found.

After about fourteen days' rest and observation hexamethonium compounds were given, in 22 patients by mouth, and in 12 by subcutaneous injection. Following discharge from hospital, usually after four weeks, patients were seen at monthly intervals for six months and thereafter three-monthly. They attended in the early afternoon, and rested in a quiet room near the ward for at least twenty minutes before the blood-pressure was recorded in both recumbent and standing positions.

ASSESSMENT OF DOSAGE

During the pre-treatment period single subcutaneous injections of hexamethonium bromide or bitartrate were given; no difference in action was discovered between the two compounds. An empirical subcutaneous dose of 25 mg. of hexamethonium bromide was given, and the blood-pressure was recorded in recumbent and standing positions at fifteen-minute intervals for three hours. The first effect was always a fall of pressure on standing and the dose was increased by 2·5 mg. amounts until the postural fall produced symptoms of faintness, or until the occurrence of other effects, such as nausea. The dose required varied from 25 to 75 mg., although often the amount which produced a well-marked postural fall had little effect on the blood-pressure in the recumbent position. This effect is shown in intra-arterial pressure tracings, where it is seen that the greatest fall took place after three minutes' standing erect, a manœuvre that had little effect on the pressure before hexamethonium was given (fig. 1). An attempt was made in this way to assess the largest dose that could be given with safety to ambulant patients, and to use that dose for treatment. There were wide variations in individual susceptibility and often a narrow margin between the amount which would produce a fall in the recumbent blood-pressure and that which would cause severe postural hypotension with symptoms of faintness and nausea. The response to single oral doses varied from patient to patient and was unpredictable, and attempts to determine a suitable dose for regular treatment were less successful. An injection of 50 mg. was considered to be roughly equivalent to 0·5 g. by mouth, although larger oral doses were often required to produce a similar effect.

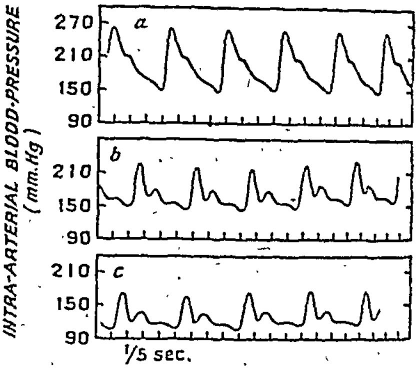


Fig. 1—Intra-arterial pressure: *a*, at rest (blood-pressure 260/150 mm. Hg); *b*, 20 min. after subcutaneous hexamethonium bitartrate 0·75 mg., with patient recumbent (blood-pressure 220/144 mm. Hg); *c*, 45 min. after hexamethonium, with patient standing for 3 min. (blood-pressure 174/108 mm. Hg).

Regular four-hourly administration by the oral or subcutaneous route was started in hospital and continued after discharge, the dose being increased at monthly visits as required, to the limit of tolerance. Patients were taught to inject the drug themselves three or four times daily. It was not considered necessary to continue treatment at night, since there is then a normal fall in blood-pressure. The oral maintenance dose varied from 2 to 6 g. a day, and the subcutaneous dose from 150 to 400 mg. a day. The increasing tolerance to hexamethonium, noted by

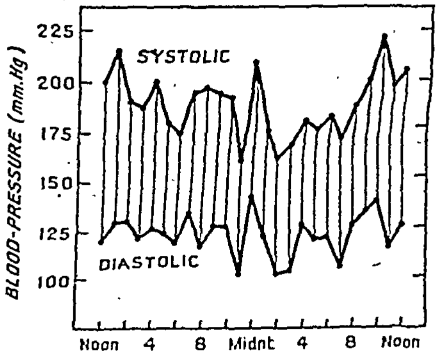


Fig. 2—24-hour variation of blood-pressure in benign hypertension.

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* A table giving the full details of the 34 cases may be obtained from *The Lancet* Office, 7, Adam Street, Adelphi, London, W.C.2.

most workers, was more obvious with oral preparations, and as much as 8–10 g. daily was given to some patients.

RESULTS

Blood-pressure

The consultation blood-pressure was higher than the admission blood-pressure in nearly all the patients.

The systolic and, to a less degree, the diastolic pressures fell during the two weeks' observation period before treatment in 29 cases, and in 25 there was a further fall during the ensuing two weeks while on hexamethonium treatment, although the amount of the fall was less than in the first fortnight on rest alone.

The weekly basal blood-pressure figures are least affected by the wide variations of pressure which take place in hypertensive patients (figs. 2 and 3), and such an average figure seems to be the only method of comparing readings made at different times in the same patient.

Analysis of the amount of fall in the different periods (table I) shows the greater change of the systolic compared with the diastolic pressure. During the period of hexamethonium treatment in hospital the systolic pressure fell less than 20 mm. in 15 cases, and the diastolic less than 10 mm. in 17 cases. This fall may have been the result of rest in hospital, or may have been due to hexamethonium therapy; longer periods of observation would have been necessary to determine the variation of the weekly basal blood-pressure in hospital without treatment. However, similar findings have been reported in a larger series of hypertensive patients treated in hospital with long periods of rest alone (Watkin et al. 1950). It therefore seemed that the hexamethonium compounds had not greatly lowered the basal blood-pressures, the fall observed being mainly due to the effect of rest in hospital.

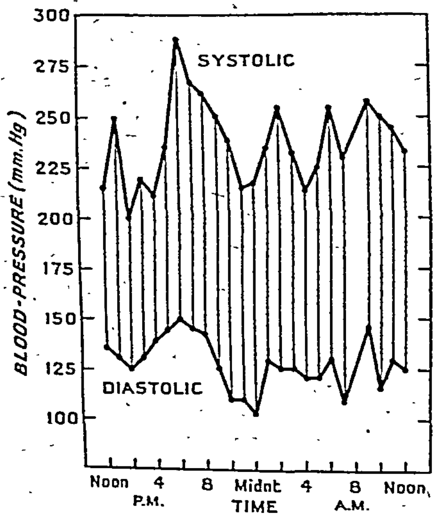


Fig. 3—24-hour variation of blood-pressure in malignant hypertension.

The readings on alternate days showed the same pattern of wide fluctuations as was seen before treatment started.

TABLE I—ANALYSIS OF CHANGES IN BLOOD-PRESSURE DURING STAY IN HOSPITAL AND AFTER THREE MONTHS' TREATMENT WITH HEXAMETHONIUM SALTS

Change in blood-pressure (mm. Hg)	No. of patients showing change: From consultation to admission		From admission to 2nd week		From 2nd week to discharge		From discharge to 3 months later	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Rise:								
Over 20 ..	1	..	..	1	1	..	13	5
11–20 ..	1	..	1	6	1	..	6	8
1–10 ..	..	6	4	..	6	8	5	12
No change ..	1	3	..	5	1	1	1	3
Fall:								
1–10 ..	6	14	4	8	8	17	5	6
11–20 ..	7	8	9	12	7	7	1	..
21–30 ..	7	3	3	..	5	1	2	..
31–40 ..	3	..	6	1	4	..	..	..
41–50 ..	3	1	2	..	1	..	..	..
51 or more	5	..	4	1	..	..	..	..

The blood-pressure had risen again to the admission level, or to that found during the second week in hospital, in most cases after one month, and in nearly all after three months, although the consultation pressures were rarely reached in follow-up readings, presumably largely because the surroundings and the observer were by that time very familiar to the patient. The blood-pressure fell on standing, often to below the narcotic level, in all the patients treated with adequate subcutaneous therapy, and in 8 of those treated with oral hexamethonium, provided the blood-pressures at outpatient attendances were taken within two hours of the last dose. In those patients who had omitted to take their midday dose because of travelling to hospital, or for other reasons, no postural fall was seen, and the blood-pressure was as high as on admission to hospital. It thus appears that the postural fall of pressure can be obtained with each dose, provided it is adequate, but that there is no evidence that the patient's blood-pressure is in fact under control.

Retinal Changes

9 patients showed severe retinal changes on admission and were classified as described by Keith et al. (1939). Definite temporary improvement in the fundi was seen in 3 cases showing papillœdema and exudates, but 2 of these patients died after nine months. The 3rd patient showed considerable improvement still present after six months although the blood-pressure was not greatly affected. In patients with milder retinal changes (grades 1 and 2) no difference was detected after treatment.

Symptoms

There was considerable symptomatic improvement after hospital treatment, half of the patients being free from any complaints at the time of discharge. The improvement in the subjective symptoms, such as fatigue and headache, was greater than the recovery from œdema or from visual disturbances. Only 3 patients were completely symptom-free at the end of the period of observation (six to nine months), but 8 patients incapacitated before treatment were living normal lives and felt much better. Not one of the severe hypertensives who showed cardiac or renal involvement noticed any lasting improvement, and by the end of nine months 7 of these patients had died. In 3 cases there was considerable temporary remission of severe symptoms of headache, nausea, and vomiting—for seven months in 1 case of malignant hypertension. No important difference was observed in those receiving hexamethonium by mouth and those receiving it by injection, although, as already described, the latter showed considerable postural hypotension. The symptomatic improvement was maintained in most patients receiving placebo tablets for short periods.

TABLE II—RENAL CLEARANCE TESTS OF CREATININE AND PARA-AMINO-HIPPURIC ACID, SHOWING THE EFFECT OF INTRAMUSCULAR HEXAMETHONIUM BROMIDE 50 MG.

Case no.	1st period (control): Urine (ml. per min.)	Clearances (ml. per min.): Creatinine	P.A.H.	2nd period (starting 20 min. after hexamethonium): Urine (ml. per min.)	Clearances (ml. per min.): Creatinine	P.A.H.
1	1·46	54	335	0·74	39·0	102
2	2·79	87	472	0·77	71·0	197
3	2·02	46	210	0·81	29·3	114

COMPLICATIONS

The complications of treatment with hexamethonium have been fully described (Turner 1950, Locket et al. 1951) and in the present series were not severe enough to interrupt treatment. Constipation was almost invariable, but was less severe when the hexamethonium was given by subcutaneous injection. Anorexia and slight nausea were common with both oral and parenteral treatment. Transient visual disturbances were common and consisted mainly in weakness of accommodation to near vision; no satisfactory antidote was found.

The most serious effect observed in several patients with impaired renal function was a considerable decrease in the amount of urine passed in the day, with profuse nocturnal diuresis. Studies of renal clearances, using a modification of the method described by Bull et al. (1950), showed a great reduction in urine flow following the subcutaneous injection of 50 mg. of hexamethonium and persisting for up to one and a half hours (table II). The effect appeared to be due to a sharp decrease of renal blood-flow, but further work is needed to determine the precise mechanism. Similar findings have been reported with other ganglion-blocking agents in normal people (Aas and Blegen 1949), and seem to be a contra-indication to subcutaneous hexamethonium in patients with impaired renal function.

DISCUSSION

Most reports on the therapeutic value of hexamethonium compounds in the treatment of hypertension have disregarded the considerable fall of blood-pressure that takes place in hypertensive patients admitted to hospital. It has been shown that this fall may continue slowly for some weeks, or may only occur after several weeks (Watkin et al. 1950). No form of treatment, therefore, aimed at lowering a raised blood-pressure can be appraised without a preliminary period of at least three or four weeks' stay in hospital. It is doubtful if the fall in pressures recorded in the third and fourth weeks of treatment can be attributed to the hexamethonium, particularly in view of the almost invariable rise of pressure to pre-treatment levels while on full dosage at home after the patient had become familiar with the technique of blood-pressure recording.

The assessment of the value of subcutaneous injections of hexamethonium compounds was regarded as particularly important, since it was clear that this was the only method of administration that could always be shown to produce a *postural* fall of pressure, and for which considerable success has been claimed in the treatment of hypertensives (Smirk 1950, Smirk and Alstad 1951). It is difficult to compare the dosages given in the present series with those used by other workers, but as far as possible the amount given was the most that could be tolerated without undesirable side-effects in ambulant patients. It was therefore disappointing to find that the fall of pressure seemed to be of the same order as in those treated with oral preparations, and that the same wide fluctuations of daily blood-pressure occurred while injections were being given three-hourly in hospital as had occurred before treatment. In comparing these results with those of other workers it must be emphasised that the blood-pressure figures quoted here were obtained in the recumbent position, since this is the normal procedure in clinical practice.

A fall of blood-pressure on standing was observed in all patients receiving adequate doses of hexamethonium and seems a possible explanation of the conflict of opinion on the value of these drugs. Restall and Smirk (1950) seem to have taken all their blood-pressure readings in the sitting position, and Murphy (1951) took his with the patient erect. This postural fall is usually observed after sympathectomy (Platt and Stanbury 1950) and is regarded as due to the abolition of normal postural reflex mechanisms maintaining blood-pressure in the sitting or erect position, and it is doubtful whether this effect alone can be regarded as "successful control" of blood-pressure in hypertension, as has been claimed.

In the present series the bromide and bitartrate salts were used in all the patients at different times, and no difference was detected in their effects; but the bitartrate was undesirable for subcutaneous use because it produced considerable local pain.

In view of the numerous substances, including injections of distilled water, which have been reported of value in the symptomatic treatment of hypertension, it would appear that almost any substance given with attention and interest to mild hypertensives may produce a remission; and, in spite of the powerful pharmacological effects of hexamethonium compounds, there still seems to be little evidence that they are of specific value in the long-term treatment of hypertensive patients.

SUMMARY

A trial, extending over six to nine months, of oral and subcutaneous hexamethonium compounds in 34 patients with severe hypertension is reported.

The variation in blood-pressure was studied in detail before treatment so as to allow each patient to act as his own control.

A considerable fall of blood-pressure took place in all the patients between the first consultation visit and the end of the control period of observation with rest in hospital alone.

A slight further fall in the basal blood-pressure took place in some patients during the period of hexamethonium treatment in hospital.

Three months after discharge from hospital the blood-pressure had returned to pre-treatment levels in all the patients, although there was considerable symptomatic improvement.

The effect on the blood-pressure was similar with oral and subcutaneous administration, except that the latter in adequate dosage always produced a postural fall of blood-pressure on standing, often to below basal levels. This postural fall was of short duration and cannot be regarded as control of the hypertension, since it seems to be solely the result of interference with normal postural reflex circulatory mechanisms.

Serious impairment of renal function directly due to hexamethonium was observed in 3 patients with malignant hypertension.

I wish to thank Prof. W. M. Arnott, Dr. E. Bulmer, Dr. W. T. Cooke, Dr. G. E. O. Williams, and Dr. K. W. Donald for permission to study patients under their care, and for their interest and encouragement. Mr. Jameson Evans kindly saw the patients showing retinal changes. The intra-arterial pressure tracing is reproduced by permission of Professor Arnott. Messrs. May & Baker Ltd. supplied the hexamethonium compounds.

REFERENCES

Aas, K., Blegen, E. (1949) *Lancet*, i, 999.
Bull, G. M., Joekes, A. M., Lowe, K. G. (1950) *Clin. Sci.* 9, 379.
Cady, J. B., Horton, B. T., Adson, A. W. (1936) *Proc. Mayo Clin.* 11, 825.
Hines, E. A. jun., Brown, G. E. (1932) *Ibid*, 7, 332.
Keith, N. M., Wagener, H. P., Barker, N. W. (1939) *Amer. J. med. Sci.* 197, 332.
Locket, S., Swann, P. G., Grieve, W. S. M. (1951) *Brit. med. J.* i, 778.
Murphy, E. A. (1951) *Lancet*, ii, 899.
Platt, R., Stanbury, S. W. (1950) *Ibid*, i, 651.
Restall, P. A., Smirk, F. H. (1950) *N.Z. med. J.* 49, 206.
Smirk, F. H. (1950) *Ibid*, p. 637.
— Alstad, K. S. (1951) *Brit. med. J.* i, 1217.
Steele, J. M. (1912) *J. Mt Sinai Hosp.* 8, 1012.
Turner, R. (1950) *Lancet*, ii, 353.
Watkin, D. M., Froeb, H. F., Hatch, F. T., Gutman, A. B. (1950) *Amer. J. Med.* 9, 428.

CARDIAC CONTUSION

IFFERENTIATION FROM CARDIAC INFARCTION

R. J. McGill
M.B. N.Z., M.R.C.P.E.

PHYSICIAN, LYMINGTON HOSPITAL, HANTS;
CHIEF CLINICAL ASSISTANT, BROMPTON HOSPITAL

It is increasingly recognised that cardiac contusion an follow direct violence to the chest. Among 75 cases f thoracic injury Barber (1944) found 20 with abnormal lectrocardiograms.

Clinically, there is remarkable similarity between ome cases of cardiac contusion and some of cardiac nfarction; and this may be of diagnostic, therapeutic, nd medicolegal interest.

CASE-RECORD

At 4.30 P.M. on May 5, 1946, an Indian soldier, aged 22, f moderate physique, fell over on a stone in the course of ustily playing a game and struck his chest in the left nipple rea. He developed persistent pain thereafter all over the nterior chest wall, especially severe in an area from he left nipple to the left border of the sternum. Soon after the accident he voluntarily passed urine and æces.

On admission to hospital at 10 P.M. he was anxious and rthopnœic. His temperature was 100°F, pulse-rate 90, and respirations 22 per min. He was tender over the 5th, 6th, nd 7th ribs in the left nipple line.

Progress.—On May 6 his temperature had risen to 102°F, pulse-rate to 144, and respirations to 46 per min. He was seen by me next day, May 7. He looked exhausted, and his accessory muscles of respiration were in action. Pain persisted unchanged, and he was spitting bloodstained watery saliva. His temperature was 102°F, pulse-rate 138; and pulse of poor volume and tension. His blood-pressure was 86/66 mm. Hg. His respirations were 32 per min. The cardiac impulse was palpable 1 in. inside the mid-clavicular line, the left border of cardiac dullness being 1/2 in. lateral to the impulse. The heart sounds were short and faint. Radiography of the chest showed no abnormality in the lungs. The heart was normal in size and shape, and there was no sign of a fractured rib. On May 8 pain was less and the patient felt stronger, but he was still coughing blood. His temperature, pulse, respiration, and physical signs were unchanged. Blood-pressure 88/70 mm. Hg. Urine examination was negative; blood examination showed Hb 80%, red cells 4,400,000 per c.mm., and white cells 11,400 per c.mm. (polymorphs 84%).

A clinical diagnosis of cardiac contusion was made.

Electrocardiography (fig. 1) on May 9 showed sinus tachycardia at 115 per min. The P–R interval was 0·12 sec. There was right axis-deviation with low voltage QRS deflections in all three standard leads, and splintering of the initial deflections in leads II and III. There was upward bowing of the ST segment in leads II and III with shallow sharp inversion of T in those leads. T in lead I was low and upright. The apical chest lead showed a Q wave, a small R wave, and a deep S wave with slight depression of the ST segment and diphasic T. A further electrocardiogram (fig. 2) on May 13 showed no significant change in rate or rhythm or in the initial ventricular deflection. The T waves, however, were then shallow, inverted in lead I and upright in leads II and III, without ST depression. The apical lead showed predominantly inverted T waves. The changes in the initial electrocardiogram indicate myocardial damage, and the ST-T changes in leads II and III and the apical lead are of the type seen in myocardial infarction but may be produced by pericarditis. The resolution of some of the changes in the succeeding five days and the development of T inversion in lead I indicate recent or active myocardial damage.

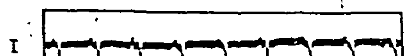


Fig. 1—Electrocardiogram on May 9, 1946.

Further Progress.—The patient's symptoms and pyrexia gradually subsided until on May 16 he was afebrile and free from pain. His pulse-rate was then 96, and respirations 28 per min., but orthopnœa persisted. There was no hæmoptysis. Blood-pressure was 90/70, the physical signs were unchanged, and a white-cell count showed 8800 per c.mm. (polymorphs 67%). The patient continued to improve and the temperature remained normal until suddenly at 1 A.M. on May 20 he developed severe precordial pain with dyspnœa and vomiting. He was collapsed, had a cold clammy skin and drawn features, and was pulseless at the wrist. The apex-beat could not be palpated, but by percussion the borders of the heart were normal. The heart sounds were short and heard with difficulty, having become much fainter than on the last examination. The heart-rate was 36 per min. with regular coupling. There was poor air entry at the lung bases. The cervical veins were not engorged, and abdominal examination was negative. Pain was relieved with morphine. The patient died at 8 A.M.

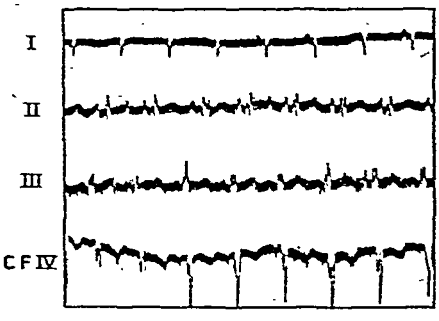


Fig. 2—Electrocardiogram on May 13, 1946.

Necropsy.—The heart was enlarged (390 g.). Pericardium normal; pericardial fluid increased, serous, and yellowish. No damage to the external surface of the heart. No trace of blood in the pericardial sac. Near the apex of the left ventricle the wall was thin. Otherwise the left ventricular wall was thicker than normal. There were extensive hæmorrhages in the middle band of muscle-fibres of the anterior and lateral walls. The right ventricle was normal. No thrombosis or occlusion of the coronary arteries was seen despite minute dissection of almost all their branches. Auricles and aorta were normal. A meticulous search was made for a lesion in the right auricle, as advised by Osborn (1943), but no abnormality was detected there. Lungs: the cut surface showed recent hæmorrhages, and serous hæmorrhagic fluid exuded on pressing; no evidence of contusion of the lung was seen. Ribs: no contusion or fracture.

Histology.—Dr. James McMurray reported as follows.

"The heart muscle shows a gross disorganisation of structure. There are healthy fibres intermingled with swollen fibres, recently necrotic fibres devoid of nuclei, and older necrotic fibres represented by granular eosinophilic debris. Spaces are also present of a pattern suggesting complete absorption of muscle-fibres. There is acute œdema, vascular engorgement, but no evidence of vascular disease. In the interstitial tissue there are many macrophages containing pigment (probably blood pigment), moderate numbers of plasma cells, and in some areas groups of polymorphs. A fibroblastic proliferation is present in relation to the areas of oldest damage which is of at least ten days' duration. The maximum damage to muscle-fibres appears to be closely arranged around the smaller blood-vessels. This would be consistent with interstitial hæmorrhages of variable extent giving rise to patchy muscle necrosis. The appearances are perhaps more suggestive of a hæmorrhagic type of infarction consistent with myocardial contusion rather than with an anæmic infarction the sequence of coronary obstruction. It is, however, realised that a dogmatic differentiation on histological grounds alone is not possible. The endocardial surface shows an organising thrombus containing many polymorphs. The findings therefore indicate progressive infarction of myocardium for at least ten days before death.

"In view of the clinical history, the absence of significant macroscopic coronary disease or obstruction, the findings of myocardial necrosis of at least ten days' duration with a pattern primarily perivascular and the presence of much blood pigment, it would seem that the cardiac lesion is one of myocardial necrosis the result of myocardial contusion. Sections show no evidence to suggest leukæmic infiltrations."

DISCUSSION

Apart from a history of injury the clinical features of cardiac contusion and cardiac infarction may be very similar; and as Barber (1944) emphasises, in cardiac injury there may be no obvious bruising of the chest wall or fracture of the bones of the thorax, this being especially true in the elastic chest of the young. The present case shows that the pain in contusion may be anginal in character; as Anderson (1940) pointed out, it is difficult to differentiate at first from the pain caused by injury to the chest wall. The same difficulty arises in cases where infarction occurs first and a chest injury afterwards. In accidents—e.g., where a motor-car driver's chest has been injured by the steering-wheel—there may have been either an infarction which led to the accident and subsequent chest injury, or a simultaneous chest injury and underlying cardiac contusion. The age of the patient is no real guide in excluding infarction. This was formerly considered uncommon under the age of 45, but Newman (1951) has recorded 100 cases between the ages of 20 and 35.

Preceding malaise or mild discomfort in the chest are features, if obtainable, peculiar only to infarction. If the lesion occurs during violent exertion, contusion is the more likely diagnosis.

Clinically, in contusion and in infarction, there may be the same collapse, with pallor and sweating, desire to pass urine and defæcate, low blood-pressure, tachycardia, faint heart sounds, and similar electrocardiograms. Inversion of the T wave, suggesting infarction, has been recorded by Warburg (1940) and by East and Bain (1948), and electrocardiographic changes were recorded in the present case. The temperature and polymorph leucocytosis return to normal similarly, and the danger period, especially in the first three weeks, is applicable to both conditions. The termination with cardiac irregularities, in this case complete heart-block with coupling, may also be similar (the coupling here was probably due to regular ventricular extrasystoles).

The formation, in the present case, of a thrombus on the left ventricular endocardial wall brings to mind a case of cerebral embolism following cardiac contusion reported by Parsons-Smith and Williams (1949). Pericardial friction may develop later (Smith and McKeown 1939, Anderson 1940). Death from pulmonary œdema is seen in both conditions, preceded possibly by hæmoptyses of varying degree. In all Osborn's (1943) fatal cases of cardiac contusion acute pulmonary œdema terminated life, where death had not been instantaneous.

It is obvious that similar degrees of myocardial impairment develop if the patient survives. Gross fibrosis in the present case would certainly have followed later. Many cases of cardiac contusion of less severity must occur and come for reassessment only in the healed and fibrotic stage. In two cases recorded by Sigler (1942) there was severe myocardial injury, and considerable cardiac disability persisted.

The difficulty in differentiating histologically between the results of coronary occlusion and trauma of the heart muscle is well exemplified in this case and is of considerable medicolegal interest.

In conclusion, caution is advised in the administration of anticoagulants where clinically and electrocardiographically the diagnosis of cardiac infarction is the most probable one but where the history of a recent chest injury is also obtainable.

SUMMARY

There is a close clinical resemblance between som cases of cardiac contusion and some cases of cardi infarction caused by coronary disease.

Features common to both are described, and a cas of cardiac contusion is recorded.

In cases diagnosed as coronary thrombosis the admini tration of anticoagulants requires caution if there is an evidence of injury to the chest.

I am much indebted to Prof. I. G. W. Hill and Dr. Kenne Robertson for their criticism and advice in the preparatio of this paper.

REFERENCES

Anderson, R. G. (1940) *Brit. med. J.* ii, 307.
Barber, H. (1944) *Quart. J. Med.* 13, 137.
East, T., Bain, C. (1948) Recent Advances in Cardiology. 4th ed London.
Newman, M. (1951) *Lancet*, i, 1045.
Osborn, G. R. (1943) *Ibid*, ii, 277.
Parsons-Smith, G., Williams, D. (1949) *Brit. med. J.* i, 10.
Sigler, L. H. (1942) *J. Amer. med. Ass.* 119, 855.
Smith, L. B., McKeown, H. J. (1939) *Amer. Heart J.* 17 561.
Warburg, E. (1940) *Brit. Heart J.* 2, 271.

RISE OF SERUM-ACID-PHOSPHATASE LEVEL FOLLOWING PALPATION OF THE PROSTATE

OWEN DANIEL
M.B. Lond., F.R.C.S.
ASSISTANT LECTURER IN SURGERY

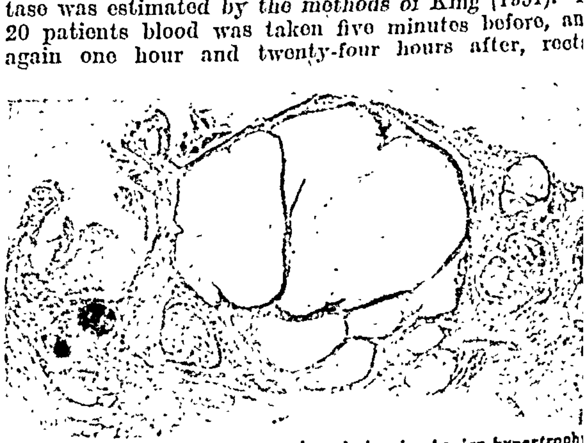
J. J. VAN ZYL
M.B. Cape Town, F.R.C.S.I
SURGICAL REGISTRAR

From the Departments of Surgery and Chemical Patholog Postgraduate Medical School of London

It has been stated that massage of a non-maligna prostate may raise the serum-acid-phosphatase to leve which suggest the presence of carcinoma of the prosta (Hock and Tessier 1949). To ascertain whether ordina digital rectal examination of the gland has a simil effect we have estimated serum-acid-phosphatase leve in 34 cases both before and after rectal palpation.

Most of the patients were in the sixth or sevent decade; 24 had benign prostatic hypertrophy, 7 ha normal prostates, and 3 had carcinoma of the prostat In 19 cases the prostate was examined histologicall and in the others the diagnosis was made on rect palpation.

The blood samples were taken from antecubital vei into dry sterilised syringes, using minimal venou occlusion. The serum was allowed to separate spo taneously, and the total and formol-stable acid phosph tase was estimated by the methods of King (1951). I 20 patients blood was taken five minutes before, an again one hour and twenty-four hours after, rect



Section of prostate (operation specimen) showing benign hypertroph with cyst formation. Formol-stable serum-acid-phosphatase level 1·7 and 2·5 units per 100 ml. before, and 8·6 units per 100 ml. an hou after, rectal palpation (× 9½).

SERUM-ACID-PHOSPHATASE LEVELS BEFORE AND AFTER PALPATION OF PROSTATE

Diagnosis	No. of patients	Age (yr.)	Serum-acid phosphatase (units per 100 ml.)					
			Before palpation		After palpation			
					1 hour		24 hours	
			Total phosphatase (normal 0·8–4·6)	Formol-stable phosphatase (normal 0·8–4·1)	Total phosphatase	Formol-stable phosphatase	Total phosphatase	Formol-stable phosphatase
ormal prostate	7	46–78 (av. 61)	3·9 (S.D. 1·3)	1·6 (S.D. 0·6)	3·9 (S.D. 1·7)	1·7 (S.D. 0·8)	2·8 (S.D. 1·6)	1·3 (S.D. 0·7)
arcinoma of prostate ..	3	76–82 (av. 78)	3·0 (S.D. 1·5)	1·7 (S.D. 0·5)	3·5 (S.D. 1·1)	1·7 (S.D. 0·4)	3·1 (S.D. 0·8)	1·8 (S.D. 0·5)
enign prostatic hypertrophy:								
Group A	21	59–79 (av. 70)	3·4 (S.D. 1·4)	1·4 (S.D. 0·6)	3·1 (S.D. 1·0)	1·7 (S.D. 0·7)	3·1 (S.D. 1·2)	1·3 (S.D. 0·6)
Group B	3	62–82 (av. 71)	3·9 (S.D. 1·4)	2·5 (S.D. 0·5)	9·7 (S.D. 1·0)	6·5 (S.D. 1·3)	5·4 (S.D. 1·6)	3·6 (S.D. 1·5)

Group A, no significant change after palpation. Group B, serum-acid-phosphatase level raised after palpation.
S.D., corrected standard deviation.

alpation. In 14 patients blood was taken twenty-four ours, twenty-three hours, and five minutes before alpation, and again one hour and twenty-four hours fter palpation. In 11 of the patients the serum-acid-hosphatase level was estimated a week before he above-mentioned tests, and 24 of the blood amples were divided into two equal parts and ssayed.

The average values of the serum-acid-phosphatase evels of each group of patients before, and one hour ind twenty-four hours after, palpation of the prostate ire set out in the accompanying table, which shows hat palpation was followed by a significant rise of the erum-acid-phosphatase levels of 3 patients with benign rostatic hypertrophy.

In these 3 cases the histological appearance of the rostate is that of benign prostatic hypertrophy with bvious cyst formation. It is possible that thin-walled ysts were ruptured during palpation and that their ontents were squeezed into the blood-stream. Prostatic ecretion is exceptionally rich in acid phosphatase, and Arner and Swedin (1949) have calculated that entry of less than 0·5 ml. of this secretion into the blood-stream could raise the serum-acid-phosphatase level to an abnormal height.

The formol-stable acid-phosphatase level in the prostate of one of the patients affected by palpation was 700 units per ml. Assuming that the secretion in the cysts contained an equal amount of phosphatase, that the volume of the patient's serum was 3·5 litres, and that acid phosphatase does not leave the circulation rapidly, we estimate that the effect produced by palpation was equivalent to the entry into the blood of about 0·3 ml. of prostatic secretion. Most of the cysts in this man's prostate have a volume considerably greater than 0·3 ml. (see figure).

In routine practice it is often convenient to take blood for serum-acid-phosphatase estimations within twenty-four hours of palpation of the prostate. The chance of producing abnormal results in about 10% of patients does not warrant a departure from this routine; but, if a raised level is found, the estimation should be repeated a few days later, care being taken not to traumatise the prostate meanwhile. A rise in the serum-acid-phosphatase level only after palpation or massage of the prostate suggests cystic benign prostatic hypertrophy.

SUMMARY

Ordinary digital rectal palpation of the prostate produced significantly raised serum-acid-phosphatase levels in 3 out of 24 patients with benign prostatic hypertrophy.

We are grateful to Prof. E. J. King for advice and encouragement; Mr. D. W. Neill, M.SC., and Miss P. Kind, B.SC., for the determinations of phosphatase; the department of pathology for the histology slides and reports; and Mr. E. V. Willmott for the photograph.

REFERENCES

Arner, O., Swedin, B. (1949) *Acta chir. scand.* 97, 135.
Hock, E., Tessier, R. N. (1949) *J. Urol.* 62, 488.
King, E. J. (1951) Microanalysis in Medical Biochemistry. 2nd ed., London.

SERUM HEPATITIS WITH RECOVERY IN SEVERE PROTEIN DEFICIENCY

J. H. DIBLE
M.B. Glasg., F.R.C.P.
PROFESSOR OF PATHOLOGY

J. MCMICHAEL
M.D. Edin., F.R.C.P.
PROFESSOR OF MEDICINE

SHEILA SHERLOCK
M.D. Edin., F.R.C.P.
LECTURER IN MEDICINE
UNIVERSITY OF LONDON

From the Departments of Pathology and Medicine, Postgraduate Medical School of London

THE prognosis of acute infective or serum hepatitis is said to be worse if the sufferer is undernourished or has some other disease. The likelihood of chronic fibrotic sequelæ is also increased (Himsworth and Glynn 1944, Fernando and Thanabalasunderam 1951). But in the following case a normal recovery followed an attack of acute serum hepatitis in a severely undernourished patient with gross hypoproteinæmia.

CASE-RECORD

A bus conductor, aged 47, was admitted to Hammersmith Hospital in July, 1942, complaining of swelling of the legs and general tiredness. There had been no diarrhœa or other gastro-intestinal symptoms. He had been operated on 20 years before for a perforated duodenal ulcer, and a gastro-enterostomy was performed at the time of closure of the perforation.

BIOCHEMICAL FINDINGS AT SIX STAGES IN THE ILLNESS

—	Range of normal values	Aug. 7, 1942	Sept. 7, 1942	Jan. 6, 1943	Jan. 21, 1943	Dec. 2, 1943	Sept. 13, 1944
Serum-bilirubin (mg. per 100 ml.)	0·5–1·0	—	—	7·7	1·3	0·5	0·5
Serum alkaline phosphatase (mg. per 100 ml.) ..	5–15	—	—	16·0	23·0	15·0	8·4
Serum-albumin (g. per 100 ml.)	3·5–4·5	2·8	3·2	2·0	2·5	2·3	0·5
Serum-globulin (g. per 100 ml.)	1·5–3·0	1·7	2·1	1·4	2·6	2·8	2·9
Bromsulphalein test (% retained)	0–10	—	—	—	12·4	0	—

The biochemical methods used were those described by Sherlock (1951).

He was a thin man with gross pitting œdema of the legs. The blood-pressure was 125/76 mm. Hg, and there was no albuminuria. The fat-content of the stools was not increased. The serum showed severe hypoproteinæmia (see table).

On Sept. 7, 1942, 1 litre of twice-concentrated human plasma was given intravenously and this led to a transient rise in the serum-protein level. The œdema decreased and the patient was discharged from hospital.

He was readmitted to hospital on Jan. 5, 1943. A fortnight previously (107 days after the plasma infusion) he had complained of anorexia, and this was followed by malaise, nausea, and vomiting. He was jaundiced and the liver was tender and enlarged 4 cm. below the right costal margin. Ascites was not detected. Gross œdema of ankles and sacrum was again present. The urine contained bilirubin but no urobilin. The biochemical findings are shown in the table.

Aspiration hepatic biopsy (Sherlock 1945) showed a severe acute hepatitis with much central disintegration of the hepatic lobules and extensive round-cell portal-tract infiltration. Cytological changes in the liver cells were severe and there was some derangement of the reticulum pattern in the lobules. Fatty change was not seen.

The patient was treated only by bed rest, and received the routine ward diet. Recovery from the serum hepatitis was uninterrupted, the serum-bilirubin level falling rapidly (see table), and he was able to leave hospital on Feb. 11, 1943.

In December, 1943, an attack of acute bronchitis again brought him into hospital, and the opportunity was taken to assess the completeness of hepatic recovery. There was no jaundice. The liver was just palpable, the edge being soft and not tender. The urine did not contain excess of urobilin. The serum-bilirubin and serum-phosphatase levels and the bromsulphalein test were normal. The peripheral œdema and hypoproteinæmia persisted. He was discharged after 4 weeks in hospital.

In July, 1944, diarrhœa began, and a barium-meal examination showed a gastro-enterostomy with rapid passage of barium along the small intestine. No stomal ulcer or fistula was demonstrated. In September, 1944, he was admitted to hospital for the last time with gross emaciation, ascites, and peripheral œdema. He became gradually weaker and died on Nov. 19.

Necropsy was restricted to an abdominal incision. It revealed a posterior gastro-enterostomy, the stomach having been united to the ileum about $7^1/_2$ ft. proximal to the ileocæcal junction. The stoma was large, about 2 in. across, and fully patent. Undigested, curd-like material was found in the ileum and was passing in this condition into the cæcum; it was slightly bile-stained. The pylorus was tightly closed, but a small quantity of well-digested chyme was found in the duodenum. There was an old ulcer scar about $2^1/_2$ in. proximal to the pylorus. The liver weighed 1800 g., and was pink and anæmic looking. There was no evidence of cirrhosis. The other abdominal and thoracic organs appeared normal. On microscopical examination the liver showed a normal lobular pattern without excess of fibrous tissue; all evidence of hepatitis had disappeared. The parenchyma showed a fairly heavy fatty infiltration, but there was no evidence of necrosis or cirrhosis.

The gastro-ileal anastomosis had caused the diversion of a considerable fraction of ingested food from the upper intestine. Although this possibility had been considered in life, it was discarded owing to the long history (20 years since the gastric operation) and the negative findings at a single barium-meal examination.

DISCUSSION

Although this patient was suffering from severe undernutrition and hypoproteinæmia, the clinical course of the serum hepatitis was uneventful. Undernutrition has been postulated as an important factor in causing chronic fibrosis after hepatitis (*Lancet* 1952). Massive hepatic necrosis resulting from protein deficiency is said to complicate the inflammatory lesion of hepatitis (Himsworth and Glynn 1944). It has even been stated that this is the only mechanism which leads to cirrhosis after hepatitis, and that, without superadded nutritional liver injury, acute hepatitis results either in death or in complete restitution of liver structure (Fernando and Thanabalasunderam 1951). Our patient was a clear candidate for massive hepatic necrosis and post-hepatitic cirrhosis if undernutrition is really a factor in their production. Recovery, however, was rapid and complete.

When cirrhosis develops after hepatitis it does so without sudden clinical or detectable biochemical deterioration. Moreover, sudden massive necrosis is not seen in aspiration hepatic biopsy sections taken during the progression of acute hepatitis to cirrhosis (Sherlock 1948). The cirrhosis following hepatitis can be indistinguishable both clinically and in its hepatic histology from the diffuse classic or Laennec type (Goldblatt 1947).

Sufferers from other diseases may be less able to withstand an attack of acute hepatitis than those previously in good health. This would be equally true of other intercurrent diseases, and acute hepatitis is not unique in its severity in such people. A high mortality-rate for infectious hepatitis is not confined to the undernourished; an epidemic of "malignant hepatitis" in Scandinavia, in which the mortality-rate was about 50%, affected well-nourished middle-aged women (Bjorneboe et al. 1948). The correlation between undernutrition and post-hepatitic cirrhosis has not been proved.

SUMMARY

A man of 47, suffering from severe undernutrition and hypoproteinæmia caused by a gastro-ileal fistula, contracted serum hepatitis. Recovery was complete, rapid, and uneventful.

REFERENCES

Bjorneboe, M., Jersild, M., Lundbæk, K., Thaysen, E. H., Ryssing, E. (1948) *Lancet*, i, 867.
Fernando, P. B., Thanabalasunderam, R. S. (1951) *Quart. J. Med.* 20, 403.
Goldblatt, H. (1947) *In* Transactions of 6th Conference on Liver Injury. New York; p. 9.
Himsworth, H. P., Glynn, L. E. (1944) *Lancet*, i, 457.
Lancet (1952) Leading article. March 1, 1952, p. 452.
Sherlock, S. (1945) *Lancet*, ii, 397.
— (1948) *Ibid*, i, 817.
— (1951) *Brit. Heart J.* 13, 273.

ACUTE FATAL RHEUMATIC FEVER IN AN ADULT

F. DUDLEY HART
M.D. Edin., F.R.C.P.
ASSISTANT PHYSICIAN, WESTMINSTER HOSPITAL; PHYSICIAN, ST. STEPHEN'S HOSPITAL, LONDON

O. A. N. HUSAIN
M.D. Lond.
LATELY REGISTRAR, DEPARTMENT OF PATHOLOGY, ST. STEPHEN'S HOSPITAL, LONDON

ACUTE fulminating rheumatic fever proving fatal in the first attack within a month of acute onset is rare at any age; in middle age it is extremely so. In a survey of the literature over the past ten years Wroblewski and Messinger (1950) did not record any such case, and Degraff et al. (1935) found that the incidence of any first attack after the age of 40 was only 4·4% of 1000 cases studied. The following case is therefore worthy of record. Additional interest lies in the fact that the patient was already under observation for another condition and so was well known to us.

CASE-RECORD

A man, aged 44, had previously been an inpatient for a fortnight in 1946, when he had no cardiovascular abnormalities but was investigated as a possible case of disseminated sclerosis; the outcome was suggestive but indefinite. There was no past history of rheumatic fever. In August, 1950, he was seen by one of us (F. D. H.) as an outpatient with various symptoms which appeared to have no basis in organic disease. His cardiovascular system was entirely normal. The Wassermann reaction and Kahn test were negative. He was then in good general health. On Sept. 29, he developed acute tonsillitis, which subsided in a few days. On Oct. 11 he felt faint and ill, and next day he developed pains and stiffness and swelling in all the joints of his extremities. On Oct. 14 he was admitted to hospital.

)n admission he was febrile (temperature 101°F). in pain, tless, and sweating. There was painful swelling in all the nts of his extremities. Albumin was present in the urine.

Progress.—In the subsequent week his heart enlarged and condition worsened in spite of full salicylate treatment d chemotherapy. On Oct. 21. pericardial friction appeared d the white-cell count rose from 9500 per c.mm. (neutroils 85%) to 25,800 per c.mm. (neutrophils 91%). Bloodltures were sterile, sputum tests and blood agglutinations re negative, and radiography showed cardiac enlargement th basal congestion. Penicillin, aureomycin, and streptorcin in succession produced no improvement. Fever persisted ound 103°–104°F; fingers, wrists, elbows, and knees were ther less swollen and painful on Oct. 26 than previously. it the patient's general condition was worse. The perirdial rub was still present, and a pleural rub had appeared the left axilla. His general condition deteriorated. and he ed on Nov. 7, 1950, comatose and bubbling, with elevated ins in the neck. (The first supplies of A.C.T.H. and cortisone rived a few weeks later.)

Necropsy showed a swarthy man of lean build with slightly rollen knees and ankle-joints. There was no clubbing peripheral cyanosis or evidence of rheumatic nodules. The heart showed generalised dilatation without hyperophy and weighed 600 g. (including thickened pericardium). displayed a pancarditis with a thick adherent fibrinous ricarditis, verrucose abacterial vegetations on the mitral id aortic valves, and histologically typical Aschoff nodes the acute stage in the myocardium.

The lungs were congested and œdematous, with early onchopneumonia, and there was a clear hydrothorax of 500 ml. on the right side and 500 ml. on the left. No evidence a rheumatic pneumonia or arteritis was seen.

The abdominal viscera showed little significant change, ere being early fatty degeneration of the liver, and in the leen a congested pulp with diminished lymph follicles.

The kidneys were congested and displayed a mild subpsular fibrosis, occasional hyalinised glomeruli, and a few attered foci of round cells in the cortex often juxtaglomerular position. No arterial lesions were detected. No gross r microscopical lesions were present in the central nervous stem, skeletal muscles, or vascular system. The kneeints and ankle-joints contained an excess of clear fluid and n œdematous and hyperæmic synovial membrane with, iiscroscopically, perivascular collections of lymphocytes.

COMMENTS

The histological picture in the heart is extremely lorid and acute, in keeping with the clinical course, hough it is well known that histological activity does iot always imply clinical severity (Mann et al. 1950).

Although the most likely diagnosis during life was icute rheumatic fever, the failure to respond to both alicylates and antibiotics and the patient's indefinite state of ill health in previous years brought to mind rarious members of the collagen group of diseases, especially polyarteritis nodosa and lupus erythematosus. No such lesions, however, were found.

The differential diagnosis is ably discussed by Grant (1951).

REFERENCES

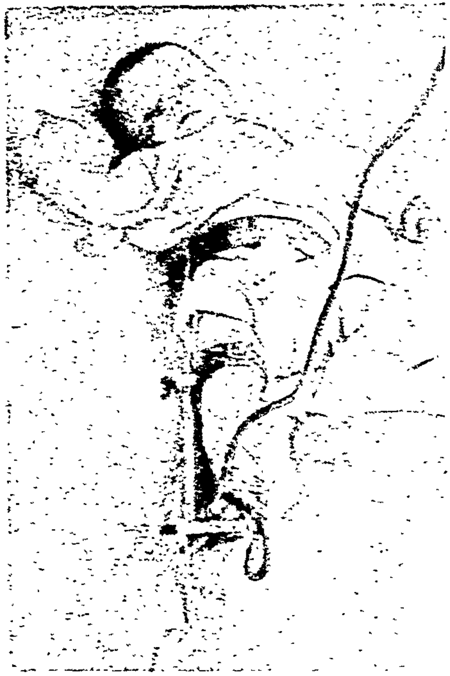
Degraff, A. C., Lingg, C., Cohn, A. E. (1935) *Amer. Heart J.* 10, 459.
Grant, C. M. (1951) Broadway (Westminster Hospital Gazette), vol. R.13: p. 100.
Mann, N. M., Rosenthal, J., Feigin, I. (1950) *Connecticut St. med. J.* 14, 902.
Wroblewski, F., Messinger, W. J. (1950) *Amer. Heart J.* 40, 345.

"... we are no longer partaking to anything like the same amount that our ancestors did of the bran or husky parts of wheat and so are deprived to a large degree of a chemical element which they contain—namely, fluorine. ... Analysis has proved that the enamel of the teeth contains more fluorine, in the form of fluoride of calcium, than any other part of the body, and fluorine might, indeed, be regarded as the characteristic chemical constituent of this structure, the hardest of all animal tissues and containing 95·5% of salts, against 72% in the dentine. As this is so it is clear that a supply of fluorine, while the development of the teeth is proceeding, is essential to the proper formation of the enamel, and that any deficiency in this respect must result in thin and inferior enamel."—Sir James Crichton-Browne, *Lancet*, 1892, ii, 7; cited by Colonel E. F. W. Mackenzie last week (p. 961).

New Inventions

AN INFUSION SPLINT FOR INFANTS

Satisfactory splinting of an infant's limb for the purpose of intravenous infusion is surprisingly difficult. The common practice is to strap the leg to a padded splint, and complete the immobilisation with wool and bandages: the splint is then finally tied to the cot. This method requires considerable care, skill, and experience, which are only too often lacking. A badly applied splint does not immobilise effectively, and the incision of the vein or the insertion of the needle is then doomed to failure. Even if adequately immobilised at the onset, a baby soon works itself loose. The needle connection is necessarily strapped to part of the splinting: therefore, if the leg is withdrawn, the needle will be left behind. Conversely, the bandage may be applied too tightly, whereupon obstructed circulation, increasing as œdema develops, is inevitable. An added objection is the constant soaking which predisposes to phlebitis, which is not readily discovered in a limb swathed in bandages.



These complications, and in particular a series of cases of thrombophlebitis, led to the design of the splint described here. It resembles a long leg-iron and works on the same principle—i.e., to immobilise a limb by preventing movement at its joints. The hip and knee are fixed by two leather belts in which a steel half-spring is incorporated. The pelvic belt is bolted to one end of a light alloy rod, along which the knee belt slides for adjustment. A foot plate is attached in the same way and, controlled by wing nuts, can be rotated in two planes to allow flexion, extension, inversion, or eversion of the foot. An extra stop can be incorporated to steady the foot plate. The end of the rod is slotted so that it can be tied to the cot.

The splint is applied merely by fastening the buckles. The foot is strapped on to the plate over a piece of felt. All the nuts are next tightened, and the leg is rendered completely immobile. The splint is interchangeable for the two legs and can be adjusted for a wide range of sizes. Apart from a simple dressing over the incision, the calf and thigh are exposed for inspection without requiring any disturbance of the apparatus. All the parts of the infusion set can be fixed directly to the limb. The child is easily kept dry, and obstruction of the circulation cannot occur. Immobilisation is accomplished without any great skill and in a short time. Removal is equally simple and rapid, and the minimum use of adhesive plaster is a factor in reducing skin complications.

Mr. Crosby, medical stores controller, University College Hospital, London, who made the entire splint in his department, can supply the technical details of construction. Mr. A. Lees, of the photographic department of the Hospital, took the photograph.

Herbert Barrie
M.B. Lond.

Dr. Robert Wells Library

Reviews of Books

Modern Trends in Gastro-Enterology

Editor: F. AVERY JONES, M.D., F.R.C.P., physician, Central Middlesex Hospital. London: Butterworth. 1952. Pp. 831. £5 5*s*.

LIKE the preceding volumes in the "Modern Trend" series which have been appearing under the general editorship of Lord Horder, this book aims at reviewing modern advances in a special subject against a background of established knowledge. Dr. Avery Jones, who edits it, has spread his net widely, and included many related fields of work, whether physiological, surgical, or medical. He makes no apology for including much that is essentially of research interest rather than of immediate clinical importance, and he offers a critical appreciation of recent progress. He has wisely refused to include some subjects on which little new knowledge has come to light, and in general his selection is excellent. Many of the 45 authors who have collaborated in this volume belong to the younger school, actively engaged in original investigations; others are more senior. On the whole the balance has been well kept between really important aspects of progress and the less significant pieces of individual research. This balance calls for skilled judgment; for a book such as this is often marred by undue emphasis on minor advances. Many of the chapters are outstandingly good; all are competent and readable. Much that is included here is not easy to find clearly elsewhere—for example, the excellent account of hiatus herniæ, based chiefly on the work of P. R. Allison, and the general review of progress in peptic ulcer by several authors. Both in its scientific and in its literary qualities this book is a fine example of British authorship. There are numerous good illustrations and full bibliographies throughout. The whole production is first-rate.

Der Dünndarm im Röntgenbild

Prof. F. KUHLMANN. Berlin: Urban and Schwarzenberg. 1951. Pp. 110. D.M. 11.80.

IN recent years more and more attention has been paid to apparent abnormalities in the X-ray appearances of the small intestine. The gross lesions of regional ileitis and tuberculosis were, of course, always comparatively easy to recognise, but disturbances of motility and alterations in the mucosal pattern were long either overlooked or ignored. Some of these abnormalities were found to be associated with deficiency diseases, allergy, and the presence of intestinal parasites, and accurate radiological diagnosis of such conditions is now a reasonable possibility. Like other workers in this field, however, Professor Kuhlmann is careful to point out that much has still to be learnt. Special techniques for small-bowel examination and the normal and abnormal appearances are very well illustrated. The German text is surprisingly clear and easy to read.

Gestation et cytologie vaginale

J. PAUL PUNDEL and FRED VAN MEENSEL. From the research laboratory of the University gynæcological and obstetric service, *Hôpital Brugmann, Brussels. Paris*: Masson. 1951. Pp. 210. Fr. 2250.

SINCE the classical demonstration of cyclic changes in the vaginal cytology of rodents by Stockard and Papanicoloau in 1917, increasing use has been made of the fact that the epithelial cells removed from the vagina reflect, in a remarkably faithful manner, the changing levels of ovarian hormones. Much has been written on the clinical application of this technique to problems of menstrual dysfunction, and more recently to the early detection of uterine and cervical carcinoma. Little has been published on vaginal smears in pregnancy, however, so the present volume fills a real need. Moreover, it does far more than merely review published work; it surveys a wide range of obstetrical problems, discusses some of the more obscure endocrinological aspects of pregnancy, carries a valuable bibliography, and contains a great deal of original work by the authors. During the first three months of gestation the vaginal smear presents varying pictures, without great diagnostic significance, but from then on, as they show, a constant appearance is the rule in normal pregnancy. Morphology of the cells, they say, is only one of the criteria to be considered; equally important are the "eosinophilic and pyknotic indices." The former requires correct staining technique with Shorr's stain and Harris hæmatoxylin. When these indices are used some of the more important complications of pregnancy—particularly threatened abortion and premature labour—can be predicted from the vaginal smear. The need for, and likelihood of success from, hormonal therapy in threatened abortion can also be decided by examination of smears.

The book also contributes to our understanding of the hormonology of the postpartum and lactation periods. The possibility of diagnosing hydatidiform mole (by finding syncytial elements) has importance for the practical obstetrician, as well as for the endocrinologist and biologist.

Management of the "Hopeless" Case

C. J. GAVEY, M.D., F.R.C.P., physician, Westminster Hospital, London. London: H. K. Lewis. 1952. Pp. 41. 9*s*.

THIS was the winning essay for the Buckston Browne prize of the Harveian Society of London in 1950, the subject being the choice of the president and council. It deals mainly with the treatment, in the widest sense, of the patient suffering or deemed to be suffering from a mortal disease, and with the doctor's attitude to death victorious or in the ascendant. It consists partly of quoted observations gathered from many sources, medical and other, and partly of Dr. Gavey's own opinions and practical advice "based on experience of cases duly recorded with this problem in view." Both constituents are admirable in themselves, though perhaps not freely miscible. There are some illuminating quotations, notably one from H. Sainsbury's *Principia Therapeutica*, a story of Osler inducing a child to greet Death as a friend, and helpful and detailed suggestions concerning drugs and operations for smoothing the way out. Dr. Gavey does not fail to point out that the field of the "hopeless" *malady is constantly* contracting *as our therapeutic armament grows, and that* "it is the hardest stone one can throw a man to remove all hope." The essay is described as "written for the student," and a thoughtful and discerning student could assuredly read it with profit. But practitioners sadly familiar with the problems with which it is concerned, can scarcely fail to find something of inspiration and help in its pages.

Metabolic Interrelations

Transactions of the Third Conference, January 8–9, 1951. Editor: EDWARD C. REIFENSTEIN. New York: Josiah Macy, Jr., Foundation. 1952. Pp. 294. $4.00.

THIS report of the Josiah Macy, Jr., Foundation's discussion group on metabolic interrelations really concerns itself with bone.

The subjects discussed are: resorption of bone: histochemical observations on the development of membrane bone; the effect of alteration in the concentration of calcium in circulating fluids on the mobilisation of calcium; osteogenesis; osteogenetic potency, and osteogenetic inductor substances of periosteum, bone-marrow, bone-grafts, fracture callus, and hyaline cartilage transferred to the anterior chamber of the eye; the effects of beryllium salts on in-vitro calcification of cartilage; inhibition of endochondral calcification in vitro by beryllium and L-histidine; effects of pituitary factors and of thyroxine on skeletal morphogenesis in the rat; the nature of bone and phosphate rock; the solubility of calcium phosphate; the rôle of phosphatase; the effect of age and low-phosphorus rickets on calcification and the deposition of certain radioactive metals in bone; retention and turnover of radiocalcium by the skeleton of large rats; and electron micrography of bone.

Some of these specialised aspects of bone metabolism are outside the sphere of interest of most physicians or even orthopædic surgeons, but Baird Hastings's observations, made about 20 years ago, on the rate at which calcium may be mobilised from the skeleton to replace an induced deficiency in the serum, are most impressive. Only 2 out of the 25 participants at the conference came from centres outside the United States.

THE LANCET

LONDON: SATURDAY, MAY 17, 1952

Hæmophilus Meningitis

SIXTEEN years ago the diagnosis of *Hæmophilus fluenzæ* meningitis was virtually a sentence of death. ie first trickle of cures began in 1937 when FOTHERLL[1] introduced his antibacterial horse-serum. EXANDER's[2] specific anti-B rabbit-serum followed 1939, and various sulphonamides were on trial at out the same time. Neither rabbit-serum nor lphadiazine alone produced spectacular results, but hen they were administered together the mortality-te was reduced to 20%.[3] Streptomycin was the next lvance, and here again combination with sulphaazine gave better results. APPELBAUM and NELSON,[4] lying chiefly on these two drugs, achieved a ortality-rate of only 3·4% in 90 cases; the survivors cluded, however, 9 children with severe residual sions. Whilst these results were being obtained in ie U.S.A., some encouraging reports on the use f penicillin in massive doses appeared in this ountry. Penicillin, despite its poor showing against I. *influenzæ* in vitro, proved in fact a useful drug gainst infection in man, and still retains a place as n adjuvant.

Three more drugs must now be added to the list of pecific agents. Aureomycin, chloramphenicol, and olymyxin passed their in-vitro and mouse-protection ests with flying colours, and recent reports have hown that each of these three can deal satisfactorily vith the infection. SCHOENBACH et al.[5] at Johns Iopkins treated a series of 30 children with proven I. *influenzæ* type B meningitis. The first group of 8 children received aureomycin, orally and intraenously, together with sulphadiazine. In the second roup there were 12 children, of whom 11 were reated with chloramphenicol alone, and 1 was given ureomycin and sulphadiazine in addition. The hloramphenicol was in general given by mouth. Of the 18 patients treated with aureomycin, 3 died, 5 were left with residual neurological damage, and 10 were cured. In the chloramphenicol group of 12, 2 were left with neurological damage and there were no deaths. SCHOENBACH points out that too strict a comparison between the groups is unwise because the average age of those treated with aureomycin was less than that of those treated with chloramphenicol. Nevertheless it seems likely that chloramphenicol will prove the better drug, for in the chloramphenicol group cerebrospinal fluid (C.S.F.) became sterile within forty-eight hours in 66% of cases, and within seventy-two hours in all cases; while among those treated with aureomycin, sterility was achieved in only 39% within forty-eight hours, and 22% still had organisms in the C.S.F. after seventy-two hours of treatment. Aureomycin does not easily pass from the blood to the C.S.F. Chloramphenicol, on the other hand, negotiates the blood-brain barrier rather better than any other antibiotic; C.S.F. levels were found by SCHOENBACH to be roughly 50% of the serum levels. Those clinicians who dislike the intrathecal route of medication may find that chloramphenicol is the drug of choice when the microcrystalline preparation for intramuscular injection becomes generally available. Those who wish to use aureomycin can now give this drug intrathecally by using the preparation described by AINLEY-WALKER and BOSANQUET.[6] Polymyxin, though successful in controlling the organism, provoked severe reactions in animals and was believed to be too toxic for clinical use. The work of SWIFT and BUSHBY[7] has shown that this is not so. They treated 7 affected children with polymyxin E and one with polymyxin B. The infection was rapidly and completely cured in all cases, although 1 child, who at first responded well, died later of intercurrent pneumococcal infection. No serious toxic reactions were encountered; and a substantial intrathecal dosage was well tolerated.

We have now, therefore, seven specific agents against hæmophilus meningitis; indeed, if terramycin fulfils the promise of its first trials,[8] there are eight. Eight drugs allow of 255 possible combinations—an *embarras de richesse* that is not without danger. Some drugs, although effective alone, may oppose one another when combined. LEPPER AND DOWLING[9] have found this state of affairs in pneumococcal meningitis. Their well-controlled study showed that when penicillin was used alone the mortality-rate was 30%; but when penicillin was combined with aureomycin the mortality-rate rose to 79%. JAWETZ and his colleagues[10] have shown an analagous conflict between the action of chloramphenicol and penicillin both in vitro and in mouse infections. The union of two antibiotics may lead to conflict, rather than an integrated action against the infecting organism; such matches should not be made unadvisedly, lightly, or wantonly. In hæmophilus meningitis cure-rates of more than 95% have been achieved in several research centres. The cure-rate in the country as a whole is probably less good and may be as low as 70%. Arguments about the merits of different régimes of chemotherapy may obscure the fact that good results rest still on early diagnosis, intensive use of the chosen drugs, and thorough treatment of complications.

Diagnosis is a two-stage process. The first stage is the recognition of the signs demanding lumbar puncture. When a child with a mild cold becomes increasingly feverish and shows gradual blurring of

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1. Fothergill, L. D. *New Engl. J. Med.* 1937, 216, 587.
2. Alexander, H. E. *Proc. Soc. exp. Biol., N.Y.* 1939, 40, 313.
3. Alexander, H. E. Advances in Pediatrics. New York, 1947; vol. 2, p. 121.
4. Appelbaum, E., Nelson, J. *J. Amer. med. Ass.* 1950, 143, 715.
5. Schoenbach, E. B., Spencer, H. C., Monnier, J. *Amer. J. Med.* 1952, 12, 263.
6. Ainley-Walker, K. M. S., Bosanquet, F. D. *Lancet,* March 1, 1952, p. 433.
7. Swift, P. N., Bushby, S. R. M. *Ibid,* 1951, ii, 183.
8. Hoyne, A. L., Riff, E. R. *J. Pediat.* 1951, 39, 151.
9. Lepper, M. H., Dowling, H. F. *Arch. intern. Med.* 1951, 88, 489.
10. Jawetz, E., Gunnison, J. B., Speck, R. S., Coleman, V. R. *Ibid,* 87, 349.

consciousness with drowsy irritability, he must be suspect: when the picture is complicated by even minimal neck stiffness or by a convulsion, lumbar puncture is imperative. The second stage is the identification of *H. influenzæ* type B in the C.S.F. This investigation is one of the few bacteriological emergencies. Treatment cannot justifiably be delayed overnight, nor await the results of culture. The direct capsule-swelling test with specific anti-B serum is a routine in many American centres, and might with advantage be used more widely in this country. Bold dosage of the chosen drugs is the factor common to the most successful series. Sometimes an over-cautious approach or fear of toxic reactions has led to half-hearted chemotherapy and hence to prolonged illness, drug-fast relapse, or permanent cerebral damage. Experience with one particular method of treatment is the ground of therapeutic courage. For this reason those who have had sustained success with, say, sulphadiazine and streptomycin may be wise to retain their familiar weapons.

The most prominent complication in SCHOENBACH's series was subdural effusions of fluid. The subdural spaces were explored whenever localising neurological signs appeared or fever persisted. This complication, which requires direct removal of the fluid, is either less common or less commonly detected in series treated with intrathecal and intramuscular streptomycin. BLOOR and his co-workers [11] found that convulsions were a common complication and carried a bad prognosis; routine prophylaxis with anticonvulsants and vigorous treatment of emergent seizures is good adjuvant therapy. Among the less common complications are drug-fast relapse and intercurrent infections, which call for a change of chemotherapy; hydrocephalic attacks, spinal block, and abscess formation, which require neurosurgical aid; and profound coma, cyanosis, and dehydration, which require the usual skilled supportive measures.

Apart from treatment, *H. influenzæ* meningitis is a problem in epidemiology. In the U.S.A. *H. influenzæ* is the commonest cause of purulent meningitis, except during epidemics of meningococcal infection. Yet hæmophilus meningitis never appears in epidemic form, and contact infections are virtually unknown. The disease shows a remarkable predilection for children between the ages of weaning and entry to school: 95% of the cases reported in Great Britain occurred in children aged more than five months and less than five years. The bacteriology is also curiously exclusive. The capsulated type-B strain is present in pure culture in the C.S.F. in almost all cases. In the nasopharynx it is a rare inhabitant. DAWSON and ZINNEMANN [12] found only 6 type-B strains in 868 swabs from healthy children; in this group of children there were 26 capsuled strains of the other types; from 468 swabs, in the same group, non-capsuled *H. influenzæ* was isolated in 384. Further study of the ecology of the disease might prove rewarding, for the incidence in this country appears to have risen sharply in the last ten years.

Meanwhile the changed prognosis of *H. influenzæ* meningitis is an index of the remarkable geometrical progression of chemotherapy. In the brief span of fifteen years we have moved from helplessness in the face of a 100% mortality to the point at which we may regard a mortality-rate above 4% as a matter for self-reproach.

Uterine Dysfunction

UTERINE action in labour is very varied and on the whole remarkably efficient; but when, occasionally, action is disturbed, the life of the child and even of the mother is in danger, and careful judgment is needed in managing the case. *The first warning* will often be prolongation of the first stage of labour, and the first duty of the attendant is to decide whether this is within or without normal limits. Many patients have niggling, ineffectual, uterine contractions for many hours, even for a day or so, yet later have easy vaginal deliveries; but alongside such cases, and not always easily distinguished from them, are others in which serious faults are present. There may, for example, be *malpresentation or unsuspected* disproportion—fœtal hydrocephaly can present in this way—or a tumour alongside or below the presenting part. In addition to these gross lesions, however, disturbances of uterine function give rise to some of the most difficult and trying abnormalities of labour.

Faults of this type *are known by many* different names—constriction-ring dystocia, colicky uterus, reversed uterine polarity, and active retention of the fœtus, together with the closely related cervical dystocia, comprising rigid cervix and conglutination of the external os. Though differing somewhat, these disturbances of uterine action have much in common; in each the cervix does not dilate, or the dilatation slows dangerously and the presenting part *advances little if at all. The cause of the* dysfunction is not known; indeed it may be impossible to say *for certain whether* the fault has originated in the upper or the lower part of the uterus, though it often seems that the lower part is the site of the disorder. Thus spasm of the muscle-fibres of the lower uterine segment or upper part of the cervix leads to constriction-ring *dystocia,* and *lack of softening* of the fibrous lower half of the cervix causes the difficulties of the rigid cervix. The seriousness of the condition is reflected in many studies. MURPHY,[1] for example, by external hysterography has recorded the activity of the pregnant uterus under many different circumstances. KARLSON,[2] by electrical recorders, has studied intra-uterine *pressure at* the level of corpus, lower uterine segment, *and* cervix, and has obtained graphic patterns of uterine motility during labour. He has made *the* important observation that, whereas in early labour the cervix and the lower uterine segment may contract independently of the *corpus*, almost simultaneous or peristaltic waves from these *three regions* can be demonstrated when labour is progressing well and the cervix is dilating. His work has been confirmed by NIXON [3] in a study of the activity of the upper segment, the lower segment and the cervix in mid-pregnancy. NIXON has also investigated the effect of pituitary *posterior-lobe* extracts, and, despite the great difficulty in comparing "in vivo" the sensitivity of muscle-fibres in different parts of the uterus, he has demonstrated differences in response from the different regions. Previous experiments "in vitro," using isolated strips of uterine muscle obtained at the time of cæsarean section, also showed differences, though these were of different character.[4] Further work is clearly required before the rôle of pituitary posterior-lobe extracts in normal and abnormal labour is understood.

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[11] Bloor, B. M., Grant, R. S., Tobris, J. A. *J. Amer. med. Ass.* 1950, 142, 241.

[12] Dawson, B., Zinnemann, K. *Brit. med. J.* April 5, 1952, p. 740.

[1] Murphy, D. P. Uterine Contractility in Pregnancy. London, 1947.

[2] Karlson, S. *Acta. obstet. gynec. scand.* 1949, 28, 209.

[3] Nixon, W. C. W. *Amer. J. Obstet. Gynec.* 1951, 62, 964.

Though we may, by careful examination, recognise disordered uterine action, we are still very far from understanding the mechanism by which it is produced. It seems that uterine function may be disturbed by even small irregularities. The occipitoposterior position of the vertex and the commonly associated high-assimilation pelvis are important, probably because they lead to uneven pressure on the lower uterine segment and cervix; for the same reason, the incompletely extended face presentation may disturb function. Minor degrees of disproportion—the result of reduced pelvic capacity or large fœtal size—and undue rigidity of the soft tissues round the vaginal vault may also affect uterine action. Fear and anxiety, though clearly undesirable and best corrected, are probably much less important than is sometimes suggested. These disorders are almost confined to primigravid women; and provided delivery is per vaginam, the dysfunction seldom returns in subsequent pregnancies. As **Jeffcoate**[5] has said, the lower part of the uterus, once stretched, never returns to its previous state.

In treatment pituitary extracts must be used with caution, and only in small amounts at a time. The slow normal labour may be accelerated by such therapy, but any incoördination of uterine action will be made worse. Management depends on sedatives, kindly control, avoidance of premature bearing-down efforts and other purposeless movements which tire the patient, administration of fluids and food, and careful observation of the maternal and fœtal condition. Cæsarean section is sometimes the safest mode of delivery for mother and child.

Pulmonary Hæmosiderosis

THE term hæmosiderosis is used to describe the deposition of the blood-pigment hæmosiderin in the body tissues. It should not be confused with hæmochromatosis,[6] which is regarded as an inborn error of metabolism characterised by excessive absorption of iron from the alimentary tract and its deposition in the form of hæmosiderin in the heart, liver, and glandular tissues; in hæmochromatosis there is also deposition of an iron-free pigment (hæmofuscin) derived from melanin.

A nutritional form of hæmosiderosis is found in African Negroes, in whom increased absorption and storage of iron (usually in the liver) is caused by an unbalanced diet of maize along with iron from the cooking-pots. In both this form of hæmosiderosis and hæmochromatosis cirrhosis of the liver is found, and the histological appearances of the lesions are similar. **Wenderoth**[7] defines genuine hæmochromatosis as an independent disease that develops slowly, in contrast to the hæmosideroses that follow or are associated with other conditions such as malnutrition, multiple-blood-transfusions, and hæmolytic anæmias. He thinks, however, that more anatomical, biochemical, and clinical data are needed to distinguish hæmosiderotic cirrhosis of the liver from true hæmochromatosis.

Hæmosiderosis of the pulmonary type is usually associated with mitral stenosis; but, as W. D. W. **Brooks** pointed out at a recent meeting of the Thoracic Society, it may arise in young men without heart-disease. Pulmonary hæmosiderosis is due to the intra-alveolar accumulation of macrophages containing hæmosiderin (siderophores or "heart-failure cells"); and in a diffuse form it is nearly always present in chronic pulmonary congestion, producing the well-known brown induration of the lungs. In the much rarer focal form repeated pulmonary hæmorrhages, either overt or intrapulmonary, are a constant feature, and the deposits of hæmosiderin in the alveoli are derived from the extravasated blood. Radiographically miliary or nodular shadows are seen. It appears that **Virchow** first mentioned this condition as long ago as 1858, but interest in it was stimulated by **Wierig**[8] and **Rosenhagen**.[9] In this country outstanding work on the clinical, radiographic, and pathological aspects of pulmonary hæmosiderosis has been done by **Lendrum**, **Scott**, and **Park**, whose results were described in a notable series of papers between 1947 and 1950.[10-16] **Lendrum**[16] says that pulmonary hæmosiderosis is of three types. The first occurs in patients with mitral stenosis; the second, described by **Ceelen**[17] in 1931 and closely studied by **Wyllie** et al.,[18] is a disease of children with anæmia but without cardiac abnormality; the third is associated with long-continued severe failure of the left ventricle.[15] Though the initial development of the cardiac-failure type differs from that of the mitral stenotic type, the histological appearances are indistinguishable; there is focal deposition of hæmosiderin (in siderophores or "heart-failure cells") in the alveolar ducts and alveoli, with stromal changes in relation to the deposits. The bleeding is believed to arise from the anastomoses between the bronchial and pulmonary circulations, in the mucosa of the terminal bronchioles; it is thought that raised pressure in the pulmonary artery produces varicose distensions of these anastomoses, through which blood easily passes. In a series of 33 necropsies on patients with mitral stenosis, focal deposits of hæmosiderin were seen in 26. The 7 cases which did not show such deposits included 6 in which there was no hypertrophy of the right ventricle, and in 5 of these there was also tricuspid stenosis. **Lendrum** remarks that it is well known that in *mitral stenosis* a tricuspid lesion seems to prevent the onset of dyspnœa and of hypertrophy of the right ventricle.

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[4] Russell, C. S. *J. Obstet. Gynæc.* 1943, 50, 287.
[5] Jeffcoate, T. N. A. *Edinb. med. J.* 1949, 101, 23.
[6] See leading article, *Lancet*, March 29, 1952, p. 650.
[7] Wenderoth, H. *Ärztl. Forsch.* 1950, 20, 549.

[8] Wierig, A. *Fortschr. Röntgenstr.* 1927, 35, 704.
[9] Rosenhagen, H. *Ibid*, 1928, 38, 353.
[10] Scott, L. D. W. *Brit. J. Radiol.* 1947, 20, 100.
[11] Park, S. D. S. *Ibid*, p. 102.
[12] Lendrum, A. C. *Ibid*, p. 106.
[13] Lendrum, A. C. *Ann. R. Coll. Surg.* 1948, 3, 32.
[14] Lendrum, A. C. *Edinb. med. J.* 1949, 56, 235.
[15] Lendrum, A. C., Scott, L. D. W., Park, S. D. S. *Quart. J. Med.* 1950, 19, 249.
[16] Lendrum, A. C. *J. Path. Bact.* 1950, 62, 555.
[17] Ceelen, W. *In* Handbuch der speziellen pathologischen Anatomie und Histologie, by F. Henke and O. Lubarsch. Berlin, 1931; vol. 3, part 3, p. 20.
[18] Wyllie, W. G., Sheldon, W., Bodian, M., Barlow, A. *Quart. J. Med.* 1948, 17, 25.

Ellman and Gee[19] have recorded 5 cases of rheumatic carditis with mitral stenosis showing *miliary radiographic appearances in the lung-fields*. Of the 5 patients 4 were young men who had had recurrent hæmoptyses. In 1 of these, hæmosiderin-containing "heart-failure" cells were present in large numbers in the sputum; in 2 others, the *aspirated lung juice showed similar cells*. In 1 case miliary radiographic shadows appeared in one mid-zone after an attack of acute pulmonary œdema; in this case also the lung fluid obtained by puncture contained numerous pigmented macrophages. Fisher and Makin[20] have lately described a case of pulmonary hæmosiderosis associated with mitral stenosis. Serial examinations established the fact that the characteristic nodular radiographic shadows took about three years to appear after attacks of pulmonary œdema or hæmoptysis. *Another valuable contribution* has been made by Danish workers,[21] who have reported 4 cases of focal pulmonary hæmosiderosis in men aged 40, 36, 27, and 51, all of whom showed the characteristic radiographic changes. Originally all 4 cases had been referred to a tuberculosis dispensary on account of suspected miliary tuberculosis. Before the correct diagnosis was made, 3 of these cases were interpreted as silicosis, and the 4th as Boeck's sarcoidosis. In 2 the diagnosis of hæmosiderosis was confirmed by biopsy of the lung during operation for mitral stenosis, and in 1 case necropsy showed pronounced focal hæmosiderosis associated with low-grade silicosis. The last case resembles Meiklejohn's[22] coalminer in whom hæmosiderosis and silicosis co-existed.

Cardiac catheterisation in 2 of the Danish cases showed that the pressure in the pulmonary artery was high at rest, and that it increased greatly after exercise. These workers state that "an increased pressure in the pulmonary circulation is unquestionably the essential pathogenetic factor in focal pulmonary hæmosiderosis." Lendrum and his colleagues also subscribe to the hypothesis of a mechanical origin, but they think that the essential cause is imbalance between the pressures of the pulmonary and bronchial circulations—i.e., the pulmonary arterial pressure need not necessarily be high. Moreover, 2 of the cases described by Ellman and Gee were also subjected to cardiac catheterisation, and in 1 the pulmonary arterial pressure was normal. They cite 2 cases reported by Laubry et al.[23] in which the pulmonary arterial pressure was not found to be raised. They go on to argue that mechanical disturbance might not wholly explain the disorder. Why, they ask, is the prevalence of the condition in mitral stenosis so low? Laubry and his co-workers say that "many cardiac cases have hæmoptyses, but few have pulmonary hæmosiderosis." Ellman and Gee, while agreeing that a mechanical cause seems the most likely, say that "we cannot dismiss the possible *implication of primary disease of vascular* elastic tissue in view of our recent knowledge that this occurs in all of the group of systemic anaphylactoid diseases of which some observers (notably Rich) have suggested *that rheumatism is but one member.*" They also agree that *pulmonary œdema can play* an important part in the ætiology of hæmosiderosis, and the case described by Fisher and Makin lends weight to Kerley's[24] contention that hæmosiderin is deposited in the lungs because *it is insoluble in* the alkaline medium of the œdematous lung. On the other hand, in some of the recorded cases of hæmosiderosis there was no radiographic or clinical evidence of œdema, and some of the patients were symptomless. But it is strange, as Ellman and Gee point out, that small hæmorrhages into the lungs *are not rapidly and untraceably phagocytosed by the* alveolar histiocytes without leaving focal deposits. It is, as they say, probably a question of speed, fresh hæmorrhages occurring before removal of the previous one is complete.

Once the focal aggregations of siderophores containing hæmosiderin are established in the lungs, they appear to be permanent; in no case have the abnormal radiographic shadows cleared. Lendrum and his colleagues have shown that round the iron deposits a fibrous *capsule* develops, which obstructs the lymphatic drainage. In some cases, as they show, calcification or ossification of the nodules takes place; and Waldenström[25] believes that there is possibly a relation between long-standing hæmosiderosis and the type of quiescent miliary infiltration which is usually diagnosed, on radiographic evidence *alone, as chronic miliary tuberculosis*. Ellman and Gee also think that there is a connection between pulmonary hæmosiderosis and the disseminated miliary ossification described by Elkeles and Glynn.[26] One *of the differences between hæmosiderosis and industrial siderosis* is that in the latter the radiographic shadows may clear after some time.[27] *Furthermore*, the inhaled inorganic iron dust or fume does *not cause* fibrosis of the lung, whereas the organic iron derived from the blood appears to be mildly fibrogenic by damaging the adjacent stroma. Apart from the "mitralised" heart-shadow seen in hæmosiderosis *there is little to distinguish the radiographic picture* from that seen in industrial siderosis.[28] In both conditions the iron deposits are opaque to X rays and the distribution of the opacities is similar, though histologically there are well-marked differences. In hæmosiderosis the aggregations of *iron* are *mainly* intra-alveolar, while in *siderosis they* are found in the *peribronchial and periarterial lymph stations.*

Many conditions *give rise* to radiographic pictures similar to that of *hæmosiderosis*; some of them are silicosis, siderosis, Boeck's sarcoidosis, miliary tuberculosis, beryllium granulomatosis, and carcinomatosis. The addition of hæmosiderosis to the already long list of conditions causing nodular or miliary radiographic shadows should strengthen the *oft-repeated* warning not to rely solely on the radiograph in making a diagnosis. The old-fashioned clinical examination may be quite useful at times.

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[19] Ellman, P., Gee, A. *Brit. med. J.* 1951, ii, 384.

[20] Fisher, R. E. W., Makin, R. *Lancet*, March 15, 1952, p. 540.

[21] Frost, J., Gormsen, H., Møller, P. F. *Acta med. scand.* 1952, suppl. 266.

[22] Meiklejohn, A. *Brit. J. Radiol.* 1949, 22, 547.

[23] Laubry, C., Lenègre, J., Abbas, L. *Acta cardiol.* 1948, 3, 91.

[24] Kerley, P. *In* Shanks and Kerley's Textbook of X-ray Diagnosis. London, 1951; vol. 2, p. 179.

[25] Waldenström, J. *In* McLaren's *Modern Trends in Diagnostic Radiology.* London, 1948; p. 86.

[26] Elkeles, A., Glynn, L. E. *J. Path. Bact.* 1946, 58, 517.

[27] Doig, A. T., McLaughlin, A. I. G. *Lancet*, 1948, i, 789.

[28] McLaughlin, A. I. G. *Brit. J. Tuberc.* 1951, 45, 105.

Annotations

THE NEW MINISTER OF HEALTH

On May 7 Mr. Iain Macleod was appointed Minister Health in succession to Mr. H. F. C. Crookshank, who comes Lord Privy Seal. As leader of a lively House of ommons, Mr. Crookshank has found the additional urden of the health portfolio a heavier load than he uld comfortably carry, and for some time it has been nown that, once the most important stages of the new ational Health Service Bill were completed, he would ish to be freed from departmental duties. The new inister probably owes his appointment at least in part his thoughtful and constructive contributions to the eliberations on this Bill. In his speeches he showed a otable grasp of the administrative structure of the .H.S., and he supported the proposed charges as a eans of redressing the balance of the different parts of e health service and not merely as an instrument of scal policy.

Mr. Macleod has sat in Parliament for only two years, ut, as the son of a doctor and a member of the Conserva- ve Party's research staff, he has a practical and theore- cal grasp of the problems of both doctors and patients.

His father, the late Dr. Norman Macleod, practised as a eneral practitioner at Skipton. He was educated at Fettes, nd Gonville and Caius College, Cambridge, and during the te war he served with distinction both as a private and as a ajor. In 1945 he failed to win a seat in the election, but the ame year he joined the Conservative Party secretariat, later ecoming head of the home affairs research department. ince he was elected to Parliament for Enfield West in 1950 e has acted as secretary, and is now chairman, of the health nd social security committee of the back benchers of his arty. He was a joint author of the pamphlet on the social ervices[1] lately published by the Conservative Party.

At the second reading of the N.H.S. Bill Mr. Macleod wisely suggested that between now and the next Budget we should study the relation which health ought to ear to the whole of our national expenditure. Most eople agree with him and regret the more that the Minister of Health is no longer a member of the Cabinet. Mr. Crookshank held Cabinet rank as leader of the House of Commons and not as the man who was responsible for the health services of the country, and this latest Ministerial change underlines the disquieting fact that health no longer claims of its own right a seat in the Cabinet. Last year, when the Ministry of Health handed over some of its duties to the new Ministry of Local Government, we were doubtful whether a small isolated and junior Ministry would have much bargaining strength at Cabinet level or in its relations with the Treasury.[2] Since then the Ministry of Education has also been dropped from the Cabinet, and now, with the deflection of Mr. Crookshank's interest, the social services are all left without even the avuncular interest of an overlord on the Cabinet. When economies have to be made, absentees are apt to come off badly; yet it is important to all of us that health and education and the other social services should have fair shares, especially of our reduced national resources.

ARTIFICIAL RESPIRATION

Usually only one method of artificial respiration is taught; but the New York Academy of Medicine has lately recommended that three methods should be known by all first-aid instructors, policemen, and mine-rescue teams. These three methods are the hip-lift/back-pressure (H.L.B.P.), the arm-lift/back-pressure (A.L.B.P.) or Holger-Nielsen, and the Silvester. Of these, the H.L.B.P. causes the greatest strain to the operator, though it also provides the greatest ventilation. The A.L.B.P., however, runs it close for ventilation, and so is useful where the patient is large and the operator small. The Silvester is useful where it is inadvisable to place the patient face-downwards, as in advanced pregnancy. There is no doubt that each of these three methods gives a far greater respiratory exchange than the prone-pressure method. All in all, the A.L.B.P. is by far the most generally useful; and in the U.S.A. it has been officially recommended by the Red Cross, the Department of Defence, the National Research Council, and the Public Health Service. It is now, also, described in the manual of the British Red Cross Society.

In the correspondence which followed our recent leading article,[1] it was suggested that movement of the diaphragm is important as a stimulus to the heart, and that by abandoning the Schafer method this valuable action would be lost. Experiment has clearly shown, however, that for resuscitation ample expansion and emptying of the lungs is more effective than a smaller tidal volume induced by diaphragmatic movement. Undoubtedly the rocking method has its uses in both acute and chronic conditions; but it is fundamentally different from the prone-pressure methods in that it has a double purpose—namely, to induce respiration, and to promote the flow of blood with the aid of gravity. The main object of artificial respiration is to fill the lungs with respirable air; and if for this purpose a single method has to be chosen, it should, we believe, be that of arm-lift/back-pressure.

TREATMENT OF DIABETIC KETOSIS

The treatment of severe diabetic ketosis varies significantly between one centre and another, the chief differences being related to insulin dosage and route of administration, early administration of glucose and alkali, and provision of additional potassium, phosphorus, magnesium, and calcium. The data necessary to settle these points are difficult to obtain. In the first place, comparison of different treatments in parallel series of cases is impracticable, owing to the relatively small number of cases treated at any one centre and the uncertainty whether control and experimental groups are in fact comparable.[2] Severe diabetic ketosis must be adequately defined; but definitions such as that of Joslin,[3] who limits the description "diabetic coma" to patients with a plasma carbon dioxide combining power of less than 20 volumes per 100 ml., nevertheless take no account of the many other features which largely determine the severity of the case. Another approach would be to assess the deficiencies of the various electrolytes by isotope dilution methods, but these would involve unwarrantable delay in giving urgent treatment. A third, and more practicable, method is to make lengthy balance observations in severe diabetic ketosis and to take the net retention of the electrolytes as a guide to the minimal losses before treatment is started. Data of this last type have been largely lacking, but the deficiency has been partly corrected by the work of Dr. Nabarro and his colleagues,[4] whose second paper on this topic is printed elsewhere in this issue.

The recommendations for treatment contained in this paper are based on detailed analysis of balance studies continued for 10–12 days after the start of treatment of cases which fall within Joslin's definition of diabetic coma. These studies showed that the extracellular fluid deficit of 20–25% was restored in less than 48 hours; and in fact sodium retention was at first excessive, with apparent transfer of sodium into cells unless potassium was replaced at the same time. Added potassium not only protects against this overloading of the cells with sodium but also prevents potentially dangerous hypokalæmia, as potassium is quickly taken up by the depleted cells and laid down with glycogen in the liver. The safe concentration of potassium in the plasma is restricted to fairly narrow limits, and the total potassium in the extracellular fluid amounts to only about 70 m.eq.; so clearly potassium must be infused with caution. Before treatment the serum-potassium tends to be high despite a total body deficit of some 350 m.eq., the reason being that the rate of loss of potassium from the cells exceeds that of its elimination in the urine. It is therefore unsafe to administer potassium before its level begins to fall in the extracellular fluid as the blood-sugar drops; and even then it should be given only if urinary flow is adequate. The patients treated by Nabarro et al. all received potassium infusions after the first 4–6 hours of treatment, and none developed serious hypokalæmia. Furthermore, no gastric dilatation and little vomiting occurred during treatment, and this may have been related to the absence of serious hypokalæmia.

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[1] See *Lancet*, Feb. 2, 1952, p. 247.
[2] *Ibid*, 1951, i, 513.

[1] *Lancet*, March 15, 1952, p. 548.
[2] Himsworth, H. P. *Brit. med. J.* 1949, i, 632.
[3] Joslin, E. P. The Treatment of Diabetes Mellitus. London, 1946.
[4] Nabarro, J. D. N., Spencer, A. G., Stowers, J. M. *Quart. J. Med.* 1952, 21, 225.

Cellular restoration was found by these workers to be divisible into three overlapping phases. In the first, water with relatively little electrolytes was rapidly absorbed by the cells as the blood-sugar, and therefore the extracellular osmotic pressure, fell. In the second stage (lasting 6–10 days) potassium, magnesium, and phosphorus were restored to the cells with more water but without an equivalent amount of nitrogen. In the third stage nitrogen was gradually restored together with proportionate amounts of intracellular electrolytes; this last stage probably occupies weeks rather than days, partly because the nitrogen intake is necessarily low early on in treatment and partly because of the katabolic response evoked by the adrenals during the stress of diabetic ketosis.[5] Low serum levels of potassium, magnesium, and phosphorus occur during the treatment of diabetic ketosis; and although no clinical syndrome can be recognised in association with low magnesium and phosphorus levels, it seems appropriate to provide these ions as well as potassium and possibly calcium [6] in the cellular repair solution that is infused.

Glucose is a powerful osmotic diuretic and must account for much of the renal electrolyte losses in untreated diabetic ketosis. Furthermore, administration of glucose during adequate early treatment with insulin and electrolyte solutions causes continuing losses of water and electrolytes, postpones cellular rehydration, and predisposes to vascular collapse.[7] It seems wisest, then, as Lee et al.[7] have pointed out, to defer administration of glucose until the blood-sugar has already begun to fall under the influence of insulin. No new data are available on the value of treatment with alkalis, but balance studies during treatment have shown that sodium and chloride are retained in the ratio in which they normally exist in the extracellular fluid—namely, 1·3 to 1 [4]—and it is therefore logical to provide them in this proportion during the early period of treatment. The solution will contain sodium lactate or bicarbonate as well as chloride, and be weakly alkalinising. Any more drastic alkali therapy carries the risk of overloading the cells with sodium [8] and leaving the patient alkalotic when the ketonæmia subsides.[9] Most important of all in treatment is the administration of sufficient doses of insulin early on,[10] for relative or absolute insulin lack is the basic disturbance. To be effective, this insulin should not all be deposited subcutaneously whence it may be poorly mobilised in a severely dehydrated patient, but is better given part intramuscularly and part intravenously. Bold yet rational treatment with insulin involves following its effect on the blood-sugar, but urine-sugar estimations may replace those of blood-sugar when Benedict's solution is no longer fully reduced.

The treatment of severe diabetic ketosis is at best an exacting procedure requiring constant skilled attention until the immediate insulin requirement has been met and rehydration achieved; but the reward promises to be a significant reduction in the high mortality.

L-FORMS OF BACTERIA

IN 1935 Klieneberger[1] isolated from cultures of *Streptobacillus moniliformis* a strange organism which differed in many respects from bacteria and which resembled the organisms of bovine pleuropneumonia. She designated this organism L1. A few years later Dienes[2] noted the development of tiny colonies similar to L1 in occasional cultures of other species; and, after Pierce[3] had shown that L1 is resistant to penicillin, similar organisms were isolated from many gram-positive and gram-negative bacteria grown in the presence of this antibiotic. Subsequently it was found that similar forms often appear in association with bacteria exposed to various bacteriostatic substances, and sometimes even when the bacteria undergo spontaneous autolysis. In a review of the investigations carried out on the L-forms of bacteria, Dienes and Weinberger[4] have now surveyed our present knowledge of these organisms.

Though Klieneberger at first held that L1 and *S. moniliformis* were unrelated organisms living in symbiosis, both she and other investigators now agree that L1 is a variant of the bacillus. In all bacteria in which L-forms have been closely studied, their formation and morphology are similar. The bacteria first swell into large bodies, which in most species have the double potentiality of developing into the tiny L-forms or of reproducing the original bacilli. It is not apparent from their morphology which course their development will take, this being determined by the cultural conditions. The L-forms grow from the large bodies as strands of small, soft, refractile granules, which have no clearly defined cell wall and which are stained with difficulty in dry films. The smallest of these granules capable of reproduction have a diameter of about 0·2 μ. On culture they may give rise to identical L-forms, or the original bacterial morphology may reappear. In most species subculture on agar leads to a continuation of the L-form, while growth in broth results in rapid resumption of the normal bacterial morphology. Occasionally—e.g., in certain strains of salmonella species—stable L-forms are produced which remain in this form despite repeated subculture in agar or broth. Though the L-forms of different bacterial species closely simulate each other both morphologically and culturally, they are related antigenically only to the parent bacteria and do not react with antisera prepared against L-forms of other species.

Transformation into L-forms is apparently always caused by an injury to the bacteria; and this raises the question whether such transformation is a purely degenerative process or whether it serves a definite purpose. This question remains unanswered, though it is noteworthy that compared with the parent bacteria the L-forms have an increased resistance to various bacteriostatic chemicals, including penicillin. This property, at any rate in vitro, is analogous to the heat resistance of spores; but there is at present no definite evidence concerning the part, if any, that it plays in the natural environment of bacteria.

L-forms closely resemble organisms of the pleuropneumonia group; and Dienes and Weinberger point out that this group are virtually indistinguishable, except rologically, from the stable L variants of salmonella. orphologically and culturally the pleuropneumonia rganisms differ so greatly from bacteria that some orkers believe that they should be classified in a different rder or even a different class. Their similarity to the -forms of bacteria, suggests, however, that they may ave evolved in the past by L-variation from bacterial arents now unknown.

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[5] Stowers, J. M. *Clin. Sci.* 1951, **10**, 487.
[6] Graham, G. *J. R. Inst. publ. Hlth Hyg.* 1950, **13**, 263.
[7] Lee, J., Naidoo, D., Torrens, J. A. *Brit. med. J.* 1949, **1**, 565.
[8] Butler, A. M. *New Engl. J. Med.* 1950, **243**, 648.
[9] Harwood, R. *Ibid*, 1951, **245**, 1.
[10] Root, H. F. *J. Amer. med. Ass.* 1945, **127**, 557.

[1] Klieneberger, E. *J. Path. Bact.* 1935, **40**, 93.
[2] Dienes, L. *Proc. Soc. exp. Biol., N.Y.* 1939, **42**, 636.
[3] Pierce, C. H. *J. Bact.* 1942, **43**, 780.
[4] Dienes, L., Weinberger, H. J. *Bact. Rev.* 1951, **15**, 245.

PREVENTION OF TRANSFUSION REACTIONS

SEVEN distinct and genetically unconnected systems of lood-groups are now recognised. Some twenty antigens re known in these seven systems, and it has been alculated that there are 46,000 possible phenotypes—dentifiable antigen compositions—of the red cell. It s only too likely that others will be discovered to swell his number; witness the "new" blood-group character lescribed by Dr. Bhende and his colleagues in our issue f May 3.[1] Fortunately, with rare exceptions, only the ABO groups and the D antigen of the Rh group are of practical importance, and careful cross-matching of patient's serum and donor's red cells should pick out any incompatibilities due to unusual antigens. Transfusion reactions from group incompatibility are now rare, and their cause is nearly always traceable: Dr. Discombe[2] has recently reported finding serological incompatibility once in about 550 transfusions, and has discussed how these mishaps could have been prevented. But exclusion of serological incompatibility does not entirely prevent transfusion reactions. Some of the other causes are now well known—for example, unsuitable anticoagulant solutions, distilled water containing pyrogens, or rubber tubing containing toxic substances. Today all properly run transfusion services take precautions against these possible dangers, but transfusion reactions still occur occasionally.

Attention has lately been focused on the possibility of allergic reactions. Miller and Tisdall[3] reported 1% of such reactions in a series of 10,000 plasma transfusions; Russell and Hess[4] had 5 such incidents in 400 blood-transfusions. These allergic reactions have been accompanied by typical symptoms—localised or generalised urticaria or angioneurotic œdema, or more severe general disturbance resembling anaphylactoid shock with respiratory distress and loss of sphincter control. These reactions usually respond to subcutaneous injection of adrenaline or a therapeutic dose of one of the anti-histamine drugs. FERRIS et al.[5] noted that the anti-histamine drugs were more effective in preventing allergic responses than in controlling them after their onset. It occurred to them that it might be possible to reduce transfusion reactions by giving a dose of an anti-histamine drug at the time of the transfusion. They describe gratifying results; not only were allergic reactions practically eliminated, but the reactions put down as "pyrogenic" were also absent.

Ferris and his colleagues used tripelennamine ('Pyribenzamine'); 25 mg. dissolved in 1 ml. distilled water was injected through the air-vent tube into the bottle of blood to be transfused, and the bottle was gently shaken to ensure even distribution. If more than one bottle of blood was being used, no more tripelennamine was given unless 12 hours or more had elapsed since the first bottle was started. With this method there were no side-effects, such as nausea, drowsiness, or headache, that could be attributed to the anti-histamine drug. Records were collected for 607 pints of blood to which tripelennamine had been added, and for control purposes similar observations were made for a series of 742 pints of blood transfused without added anti-histamine drug. In the tripelennamine series there was 1 case of allergic reaction, no pyrogenic reaction, and 1 case of hæmolytic reaction—a total of 2 (0·32%). In the control series there were 20 cases of allergic reaction, 32 cases of reactions classed as pyrogenic, no hæmolytic reaction, and 1 unclassified reaction—a total of 53 (7·16%). This last figure is high, but Ferris points out that the resident staff were on the look-out for reactions, and he says, with justice, that ordinarily most relatively mild reactions go unrecorded. He cites the case of a man with hæmophilia who had had many transfusions and suffered many allergic and pyrogenic reactions—in the hosptial where Ferris and his colleagues were working he had had 3 severe reactions in four days. This patient was given 50 mg. tripelennamine intramuscularly one hour before the start of each of the next 4 transfusions, and no reactions occurred. Another patient developed severe generalised urticaria after receiving 100 ml. of blood; 100 mg. of tripelennamine was given orally and the urticaria died down in an hour; the transfusion was then re-started, and the remaining 400 ml. of the same blood was given without incident.

It is important to note that the so-called pyrogenic reactions were eliminated along with the definitely allergic reactions; this effect was not expected by Ferris and his co-workers. It has often been observed that when there is a transfusion reaction, even a non-hæmolytic one, the effect of the transfusion on the blood-level is less than expected. The administration of an anti-histamine drug is safe and simple, and it seems worth while to give it a trial particularly in patients who are having multiple transfusions and have a history of previous transfusion reactions. Any method which reduces the incidence of transfusion reactions will not only benefit the patient, but will save blood by ensuring the maximum effect.

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[1] Bhende, Y. M., Deshpande, C. K., Bhatia, H. M., Sanger, R., Race, R. R., Morgan, W. T. J., Watkins, W. *Lancet*, May 3, 1952, p. 903.

[2] Discombe, G. *Ibid*, April 12, 1952, p. 734.

[3] Miller, E. B., Tisdall, L. H. *J. Amer. med. Ass.* 1945, 128, 863.

[4] Russell, W. K., Hess, F. T. *U.S. Navy med. Bull.* 1945, 95, 725.

[5] Ferris, H. E., Alpert, S., Coakley, C. S. *Amer. Practit.* 1952, 3, 177.

ERYTHEMA NODOSUM

ERYTHEMA nodosum is commonly regarded as a reaction to various infections and drugs. Miescher,[1] in a histological study of cases due to a variety of agents, found a peculiar arrangement of histiocytes. This suggested to him that the syndrome was a disease entity, and was probably due to a virus infection. He compared it with herpes simplex, which can be provoked by various circumstances.

In a useful review Doxiadis[2] concludes that erythema nodosum is a disease of allergy and suggests that the peculiar histology may be determined by the site—the deep dermis and hypodermal fat. He insists that infection is a prerequisite in all cases, including those apparently provoked by drugs, such as sulphathiazole. The causative infections vary with age and habitat. In European children 50% of cases are said to be associated with primary tuberculosis, the eruption commonly accompanying the development of skin sensitivity to tuberculin; the skin lesions appear three to eight weeks after exposure to an open case of tuberculosis, and physical or radiological evidence of tuberculosis, if not found at the time of the rash, appears within six months. Attention to the likelihood of underlying tuberculosis should not be distracted by the presence of other infections. These may act in two ways: either as added provocation, or by temporary depression of the tuberculin sensitivity. This sensitivity soon regains its former intensity when the acute infection is over, and erythema nodosum may then appear. Similarly, sulphathiazole more commonly causes this eruption in tuberculous children than in others.

Curiously enough, erythema nodosum is rarely found in children inoculated with B.C.G.[3]; and tuberculosis workers find difficulty in excluding spontaneous infection with virulent tubercle bacilli in the few such cases they see. This rarity is thought to be due to the comparatively weak hypersensitivity induced by B.C.G. On the other hand, where enormous doses of B.C.G. have been accidentally injected[4] a high degree of tuberculin sensitivity has been produced without the appearance of erythema nodosum. As with all allergic phenomena, individual susceptibility is clearly important. Erythema nodosum is relatively more common in women than men. This, and its occurrence on the legs, leads Doxiadis to suggest that it may be related to the difference in clothing between the two sexes. This female preponderance has been noted, however, since Victorian times, when, we are told, even the legs of pianos were heavily draped. Sometimes erythema nodosum is associated with pulmonary infiltrations and hilar adenopathy. In some cases this is due to primary tuberculosis; but in others the infiltration is bilateral and transient, and these changes are associated with anergy to tuberculin and are followed by a radiological picture of sarcoid. The similarity of such cases to coccidioidomycosis led Kerley[5] to postulate a specific infective cause in sarcoid, possibly a fungus. Löfgren,[6] who did much to clarify the significance of tuberculosis in erythema nodosum, finds sarcoid a chief cause of the rash in Stockholm, now that the incidence of tuberculosis has been reduced. The extreme rarity of erythema nodosum in leprosy is possibly further evidence against the hypothesis that sarcoid is caused by Hansen's bacillus.

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[1] Miescher, G. *Schweiz. med. Wschr.* 1948, 78, 269.

[2] Doxiadis, S. A. *Medicine, Balt.* 1951, 30, 283.

[3] Conference on European B.C.G. Programmes. London, 1951.

Much of the evidence for allergy as a cause of erythema nodosum is indirect. In a fatal case reported by Sonck[7] vascular lesions of the brain were reminiscent of the Sanarelli-Shwartzman phenomenon. Again, the suppression and possible cure of erythema nodosum by cortisone[8,9] suggests—but does not prove—that the process is allergic rather than infective. The list of affections with which erythema nodosum has been associated reads like a hypochondriac's nightmare, for it ranges from lymphogranuloma inguinale to cat-scratch disease. Some dermatologists maintain that really classical erythema nodosum, which is rare, is a disease per se, without discoverable cause. Loewenthal[10] described a case in which the lesions were induced by the patient's feelings of hostility towards his mother-in-law. The symbolism is clear, bearing in mind the appearances which gave the disorder its synonym of dermatitis contusiformis.

MONTESSORI

We probably learn faster in our first five years than at any other time of our lives, thanks to the active curiosity of our minds and the increasing mobility of our persons. Dr. Maria Montessori, who died on May 6 at the age of 81, was one of the first people to suggest that this early capacity and taste for learning should be allowed plenty of scope. The system of education which bears her name brought great refreshment to teachers everywhere, and has given thousands of children an interesting start in life.

She was a remarkable woman in many ways. She was born at Chiaravalle, Ancona, in 1870, the only daughter of Cavaliere Alessandro Montessori. Her interests were scientific, and she entered the University of Rome as a medical student, and was the first Italian woman to take a medical degree. Her first job was in the training of mentally defective children, and as so often happens in medicine her studies of the abnormal threw light on the normal. Training is more important than treatment for mental defectives, and given the right chances they are as willing as normal children to learn to the full extent of their capacity. Dr. Montessori was able to put some of her eight-year-old defectives in for the State examination in reading and writing; they passed, and in fact did better than some of the normal children. In 1907 she had the opportunity of applying her principle, which might be called "liberty to learn," to normal children. The Istituto Romano di Beno Stabili took in hand the slum district of San Lorenzo, and attached a *casa di bambini* to each block, and Dr. Montessori was put in charge of them. The children did splendidly and her method became established and widely accepted. She acted on the belief that children are so eager to learn movements and so eager to copy those around them that if they see good and courteous behaviour round them they will pick it up. "A child will learn good table manners," she once wrote, "as soon as he can control his muscles, if you first show him how to hold a spoon and then have a little patience while he tries his best and spills things everywhere. As soon as the muscles are under control the spilling will stop." It is a measure of the success of her teaching that this is nowadays accepted practice in almost every home. We no longer expect children to learn everything at once.

She also thought of the child as a little scientist, engaged in constant experiment, and badly in need of the necessary equipment. So in her schools the chairs and tables were made to fit the children, and they were free to move about as their interests and activities called them. She developed a great deal of equipment, all designed to teach the child through his natural curiosity. The famous pink tower is a typical example: it consists of 10 bricks painted pink, the largest a 10 cm. cube, the smallest a cube of 1 cm., which can be piled into a pinnacle. The child who has played with these bricks has unconsciously learned to appreciate a great many things about size, colour, weight, and shape. When his arithmetic teacher says to him, later: "A cubic centimetre is just the size of the smallest brick in the pink tower" the image is ready for recall. Dr. Montessori let children learn muscular coördination by knocking graded pegs into the holes in a wooden block, and let them learn the beginnings of arithmetic by arranging series of graduated wooden rods. The child's own eye corrected his errors. Sensory training included matching coloured silks, pairing different materials blindfold, and detecting the differences in bells; the alphabet was learned by sight and touch from rough-surfaced letters stuck to a card. Geometry could be learned from cut-out metal figures which would take to pieces. The theorem of Pythagoras becomes plain in a moment when the appropriate parts can be removed and fitted into the disputed area. Mathematics can be tackled on these terms by children under five, and a very good idea they get of it. When the children tired of a subject it was dropped for the time; but they tired much less easily than might be expected, though after a period of concentration they needed to relax. The child, she held, was the best judge of his pace: "If he is ready for arithmetic from 9 to 9.30 in the morning, it is highly unlikely that he will have any interest in writing or anything else from 9.30 to 10." There were no rewards or punishment in her schools; there were also no fairy-tales, though there were plenty of animal stories.

Her books on scientific education were translated into many languages and her methods widely accepted, not only in Italy and elsewhere on the Continent but in Great Britain and America. She travelled widely, demonstrating and lecturing, and often visited this country to give training courses under the ægis of the British Montessori Society. In 1923 she was given the honorary degree of D.LITT. by the University of Durham. The details of her method are less widely accepted today than they once were, but the principle that the child should have freedom to learn and to develop his muscles and senses is still widely applied in all our nursery schools. It is a principle worth holding fast.

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4. Imerslund, O. *Acta tuberc. scand.* 1943, 17, 282.
5. Kerley, P. *Brit. J. Radiol.* 1942, 15, 165.
6. Löfgren, S. *Nord. Med.* 1951, 46, 1069.
7. Sonck, C. E. *Hautarzt*, 1951, 6, 279.
8. Ureles, A. L., Kalmansohn, R. B. *New Engl. J. Med.* 1951, 245, 39.
9. Farber, S., Mandelbaum, H. *Arch. intern. Med.* 1951 88, 395.
10. Loewenthal, L. J. A. *Brit. J. Derm.* 1949, 56, 403.

Medical Conferences

AMERICAN COLLEGE OF PHYSICIANS

THE 31st annual session of the American College of Physicians was held at Cleveland, Ohio, from April 21 to 25. This consisted of a series of lectures on general topics of interest to the physician; four symposia on thyroid disease, hypertension, diabetes, and rheumatic fever; fifteen panel discussions on various topics; clinicopathological conferences; demonstrations of cases by colour television; and clinical discussions of patients at the various hospitals in Cleveland.

Immunity to Poliomyelitis

Dr. JAMES GEAR, deputy director, South African Institute for Medical Research, in the James D. Bruce lecture indicated that the day is fast approaching when [illegible]s will be prevented. [illegible] his observations on poliomyelitis among the European and Bantu populations in South Africa and reviewed pertinent studies on epidemics of poliomyelitis outside Africa. In essence, he found by *testing antibodies* and by study of *virus in stools that* the incidence of poliomyelitis infection depended on the immunity in the exposed populations. In primitive populations where hygiene and sanitation were poor, infection was widespread and new cases appeared only in infancy and childhood. In populations where the standards of hygiene were high the population was virtually without immunity, and during epidemics cases developed in adults as well as children. This was true in South Africa during the epidemics of 1945 and 1948, and was also seen in the Middle East during the late war. His data showed that 90% of adult Bantus have immunity to the Lancing strain of poliomyelitis. 72% of infants have neutralising antibodies in their blood, and these are presumably transmitted through the placenta. In the recent epidemic in South Africa there were 10 times as many cases in Europeans as in Bantus, although the Bantus outnumber the Europeans by 6 to 1. Dr. Gear felt that there were precipitating factors in the development of poliomyelitis. These were related to fatigue, operations on the mouth and throat, pregnancy, and the injection of vaccines and other substances parenterally. He believed that the virus of poliomyelitis acted in many ways like the virus of yellow fever, and that very shortly we would have an attenuated virus which could be used for protection against poliomyelitis. Enders has recently produced avirulent strains of poliomyelitis virus by growth in human and monkey tissue-cultures. In conclusion Dr. Gear said that poliomyelitis was at present a disease of civilised communities, and it was clear that of all who contract the infection only a minority develop paralysis.

Histoplasmosis

Dr. AMOS CHRISTIE, professor of pædiatrics, Vanderbilt University School of Medicine, said that histoplasmosis is especially prevalent in the central part of the United States between the Appalachian and the Rocky Mountains, and the yeasts have been found in the soil in this area. Four types of disease are recognised: a benign pulmonary infiltration, a disseminated progressive disease, healed lesions (especially in the lung), and intermediate forms. The disease is most commonly confused with tuberculosis, but the tuberculin test is always negative. Pathologically there is reticulo-endotheliosis with giant-cell formation, caseation, and blood dissemination. He described some cases which simulated tabes mesenterica, ulcerative colitis, and subacute aleukæmic leukæmia in children. He also described a case of Addison's disease due to histoplasmosis. 50% of patients with active disease have ulcers of the skin or mucous membrane, especially in the oropharyngeal region. Besides skin tests, biopsies can be screened by use of the Hotchkiss MacManus stain which brings out the polysaccharide in the histoplasma very clearly. The only therapeutic agent of value is ethyl vanillate, which is toxic and not very satisfactory.

Ballistocardiography

Dr. ISAAC STARR, Hartzell research professor of therapeutics, University of Pennsylvania School of Medicine, invented the ballistocardiograph fourteen years ago; and at the meeting he described the high-frequency and low-frequenc[illegible] (both of which are moving-table [illegible]nd also discussed the new portable [illegible]ented by Dr. W. Dock. This new machine consists of a bar of metal which is placed across the lower limbs of the patient, who lies on a floor or rigid bed. The pulsations of the bloodstream move the bar, and the changes are recorded electrically on the portable electrocardiograph equipment. Dr. Starr described some experiments with cadavers in which he simulated the movement of the blood column in life by sudden injection of fluid into the arterial tree. With this instrument he reproduced and isolated various phases of the ballistocardiographic tracing and analysed the tracing in terms of strength of ejection of blood and the damping effect of the body mass. He described cases in which abnormal ballistocardiographic patterns were obtained in the presence of normal clinical and electrocardiographic findings. Later these patients developed clinical heart-disease. Dr. Starr believes that the ballistocardiograph will be extremely useful in the future for screening patients for evidence of cardiac weakness and for preventing cardiac disease through early therapy.

Blalock-Taussig Operation

Dr. HELEN B. TAUSSIG, associate professor of pædiatrics, Johns Hopkins University School of Medicine, discussed her analysis of the first 1000 Blalock-Taussig operations, 857 of which were done for the tetrad of Fallot. The results were excellent in 773 cases, and fair in 39; there was no improvement in 31; and 157 patients died during or shortly after the operation. The mortality-rate in the tetrad of Fallot was less than in other conditions.

Interatrial Septal Defects

Dr. CHARLES P. BAILEY, professor and head of the department of thoracic surgery, Hahnemann Medical College and Hospital of Philadelphia, described recent work in his clinic on the repair of interatrial septal defects by an intracardiac plastic operation.

Angiocardiography

Dr. CHARLES T. DOTTER, assistant professor of radiology, Cornell University Medical College, discussed angiocardiography in mediastinal and pulmonary disease. Angiocardiography, he said, is especially useful in differentiating between vascular regions associated with the heart and non-vascular mediastinal masses. Unfortunately, there were no typical appearances in patients with early or late neoplastic disease of the lung, and angiocardiography was of no value in making a differential diagnosis between the various types of solitary lesions found in the lung.

Sodium Studies in Hepatic Cirrhosis

Dr. WILLIAM J. EISENMENGER (Hospital of the Rockefeller Institute for Medical Research) pointed out that, while Ralli had found that glomerular filtration was low in hepatic cirrhosis, normal filtration-rates had been observed by other investigators, particularly Epstein. In his own studies he found that the specific gravity of the urine dropped when the patients were placed on a low-sodium diet, and this was accompanied by diuresis. He also found that patients with cirrhosis and ascites had a delayed diuresis with water-loading tests. He suggested that his observations indicated that cirrhosis caused an increased production of antidiuretic hormone, and that this was the cause of ascites in cirrhosis.

Latent Steatorrhœa

Dr. DOUGLAS G. CAMERON, assistant professor of medicine, McGill University, described six cases with various clinical manifestations of steatorrhœa, such as tetany, osteomalacia, megalocytic anæmia, and iron-deficiency anæmia. All these patients gave histories of normal bowel function, and none of them had diarrhœa or passed bulky stools. However, when tested with a diet containing 75 g. fat, they excreted 11–36% of the fat intake. Their nitrogen excretion was normal; and Dr. Cameron held that these were cases of latent steatorrhœa.

Splenic Flexure Syndrome

Dr. THOMAS E. MACHELLA, assistant professor of medicine, University of Pennsylvania School of Medicine, described a syndrome in which the function of the splenic flexure was disturbed by spasm and trapping of gas. He studied 40 patients (19 males and 21 females) in whom this disturbance produced a feeling of pressure and fullness in the precordium, shortness of breath, and palpitation. The pain was relieved by passing stools or flatus or by changing position. The precipitating factors were emotional disturbances, constipation, meals, and lying down. It was important to recognise this splenic flexure syndrome and to distinguish it from coronary heart-disease.

Cat-scratch Disease

Dr. WORTH B. DANIELS, professor of clinical medicine, Georgetown University School of Medicine, remarked that cat-scratch disease is becoming quite an important condition in clinical practice in the United States. He described 60 cases and 7 household epidemics. The enlarged glands persisted for up to 6 months but were usually gone by the end of 6 weeks. Intradermal tests were very useful in diagnosis, but unfortunately the batches of antigen varied. He believed that the syndrome described by Parinaud—conjunctivitis and an enlarged pre-auricular gland—was a variety of cat-scratch disease in which the agent entered the body through the conjunctiva.

Hypertension Treated with Protoveratrine

Dr. SIBLEY W. HOOBLER, assistant professor of internal medicine, University of Michigan Medical School, reported that protoveratrine given by mouth was useful in treating hypertensive patients for long periods, since it produced no side-effects.

Anticoagulants in Congestive Heart-failure

Dr. GEORGE C. GRIFFITH, professor of medicine, University of Southern California School of Medicine, found that in 565 patients with rheumatic heart-disease in failure, death was due to thrombo-embolism in 114 (21·3%). He therefore decided to treat patients with congestive failure with different anticoagulants, in order to determine whether these were effective in reducing mortality. He studied 804 cases of congestive failure—213 were used as control cases, and the remainder were treated with heparin or dicoumarol or 'Tromexan.' The final outcome was unsatisfactory in 32% of the control cases, but in only 10% of the treated cases. Thrombo-embolic phenomena occurred in 33% of the control cases but in only 7% of the cases treated with one of the three drugs. Statistical analysis showed that there was no difference between the effectiveness of the three drugs in controlling thrombo-embolic phenomena.

External Pancreatic Secretion

Captain JOHN M. HOWARD (Army Medical Service Graduate School, Washington), together with Dr. Evans of the South Western Medical School, studied a soldier who had a draining pancreatic fistula as a result of a bullet wound received in Korea.

In careful studies they showed that a meal in the stomach had a greater effect in producing pancreatic secretion than an acid meal injected directly into the duodenum or jejunum. Surprisingly, oral alcohol depressed the secretion of juice, while intravenous alcohol had no effect on pancreatic secretion. Neostigmine increased the flow of juice, and atropine and 'Banthine' depressed it slightly. Administration of ephedrine suppressed the secretion of juice. Banthine blocked the effect of a test meal in increasing the pancreatic secretion, but neither banthine nor atropine blocked the effect of secretin.

Meals in the stomach were very effective in producing secretion of pancreatic juice, and partial gastrectomy might be a rational treatment for chronic recurrent or relapsing pancreatitis. Neither aureomycin nor streptomycin appeared in the pancreatic juice after therapeutic doses were given to the soldier, but penicillin appeared rapidly in high concentration after injection. Thus penicillin was the antibiotic of choice in the treatment of pancreatic disorders. Treatment of acute pancreatitis should consist in gastric suction, withholding oral fluids and food, and administration of banthine or ephedrine and parenteral penicillin.

Endocrine Relationships of the Thyroid

Dr. JAMES HOWARD MEANS, Jackson professor of clinical medicine, Harvard Medical School, reviewed briefly the various hormonal substances which affect the thyroid and showed how antithyroid drugs block uptake of iodine or production of thyroxin. He outlined the need for a therapeutic agent to suppress the thyroid-stimulating hormone (T.S.H.) and suggested that the new compound recently reported by Gross and Pitt-Rivers[1] might be the first effective anti-T.S.H. drug.

Dr. Means introduced Sir CHARLES HERCUS, who pointed out that although New Zealand was surrounded by sea the soil levels of iodine were 1000 times greater then the iodine-levels in the sea. Yet, this was not enough to prevent goitre in man, sheep, or other animals. The epidemics of goitre in sheep were related to their ingestion of goitrogenic plants of the genus brassica. In New Zealand goitre did not appear in the first generation of settlers but occurred in the second generation of New Zealanders. In New Zealand he found a positive correlation between goitre and hyperthyroidism, but carcinoma of the thyroid was extremely rare. In recent studies on rats he has produced nodes in the thyroid glands by feeding with brassica. These nodes were transplanted into other rats, and were shown to be under the control of the pituitary through T.S.H. *Some of the nodes*, however, became malignant; the *malignant* nodes were not under the control of the *pituitary*, and T.S.H. had no effect on them.

Treatment of Hyperthyroidism

Dr. ELMER C. BARTELS (Lahey Clinic, Boston) described a series of 2400 patients who were seen at the Lahey Clinic during the past eight and a half years. These were studied by two physicians and operated on by nine surgeons who used the standard Lahey technique. 20% of the patients had adenoma with thyrotoxicosis, and the remainder had Graves's disease; 10% had cardiac complications. All patients were treated with various types of antithyroid substance and were brought to a euthyroid state before surgery. Propylthiouracil was used in 1500 patients, of whom 1% developed agranulocytosis. Lugol's iodine was given to patients with primary Graves's disease but not to those with adenoma. The cholesterol level was much more satisfactory than the basal metabolic rate for deciding when the patients had returned to a euthyroid state. The over-all mortality-rate was 0·2%; deaths were due to cardiac arrest or to respiratory arrest. Bartels believes that the respiratory arrest can be prevented by doing a tracheotomy routinely in all patients with Graves's disease and cardiac involvement prior to operation on the gland. 10% of the patients developed myxœdema. Pregnancy did not interfere with the plan of treatment. In pregnant women Bartels protected against fœtal loss by giving Lugol's iodine and thyroid after the operation. In the pregnant they were careful not to operate if the patient developed myxœdema while on antithyroid drugs; they stopped the drugs and waited for the cholesterol level to return to normal before operating.

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[1] Gross, J., Pitt-Rivers, R. *Lancet*, 1951, ii, 767; *Ibid*, March 1, 1952, p. 439; *Ibid*, March 22, 1952, p. 593.

ANTITHYROID DRUGS

Dr. Samuel Asper, assistant professor of medicine, Johns Hopkins University School of Medicine, said that in 95% of 291 patients excellent results were obtained from a daily dose of propylthiouracil varying from 150 mg. in mild cases to 400 mg. in severe cases. The return to the euthyroid state took from three weeks to three months. He found no advantage in concomitant iodine therapy, and only 2 of his patients developed an agranulocytosis. This occurred eighteen months after treatment was started, and the patients' blood was restored to normal after therapy with cortisone. Most of the failures were due to the fact that some patients refused to take propylthiouracil every day; it was most important to see that effective therapy was given day by day. Only 2 patients were completely refractory to therapy; these had hypertension in association with their thyrotoxicosis, and they were treated satisfactorily with radioactive iodine. In 48 patients the drug was stopped, and in 24 of these there was a relapse. The goitre decreased in size in 60% of patients, was unchanged in 35%, and increased in 5%. Exophthalmos did not regress in any patient, nor was progression seen. He described 5 young women with large thyroid glands and tremendous bruits over the glands. These girls were in their 'teens and rather tall and well developed. Although their basal metabolic rate returned to normal after therapy with propylthiouracil, the bruits continued to be heard and the glands did not change in size.

RADIOACTIVE IODINE

Dr. Perry McCullagh (Cleveland Clinic) has treated 640 patients with hyperthyroidism, many with recurrent Graves's disease (after surgery), and many with cardiac complications. Most of the patients were over 40 years old, and 98% were free of hyperthyroidism six months after receiving I^{131}. The most difficult part of the therapy was to decide on the amount of radioactive iodine to use. In nodular goitre the average curative dose was 34 millicuries, and in primary hyperthyroidism they used 100–200 microcuries per g. of thyroid (assumed weight) with an average dose of 10 millicuries for a 60 g. gland. Radioactive iodine was not used in pregnancy; but there was not any danger in giving it to a woman in the first two months of pregnancy, since the fœtal thyroid does not concentrate iodine or radioactive iodine in the first two months. 10% of patients developed myxœdema, but this figure was no greater than that in series treated surgically. Therapy with radioactive iodine had many advantages. There had been no deaths, no vocal-cord involvement, and no tetany; the thyroid size was reduced; and there were few recurrences. Moreover, radioactive iodine was the cheapest form of therapy. The danger of neoplasms developing in patients treated with radioactive iodine had, in Dr. McCullagh's opinion, been over-emphasised.

Special Articles

RUNNING THE HOSPITALS

JUBILEE CONFERENCE

The Institute of Hospital Administrators began in 1902 as the Hospital Officers' Association. The present title was adopted in 1945 after a single professional society for hospital administrators of all kinds had been formed by union with the Association of Clerks and Stewards of Mental Hospitals. The fiftieth anniversary of the society was marked by a jubilee conference in London, which was opened on May 8 by Miss Patricia Hornsby-Smith, parliamentary secretary to the Ministry of Health.

Rôle of the Central Department

At the first session Mr. J. E. Pater, an under-secretary at the Ministry of Health, traced the development of the hospital service from the time, fifty years ago, when the name "hospital" was restricted to a place where the infectious could be isolated, and when workhouses and infirmaries were controlled by voluminous regulations issued by the central department of the time—the Local Government Board. The board was sufficiently interested in detail to decree that the diet of the poor and the sick should be supplemented for two days to celebrate the coronation of King Edward VII; but there was no statutory duty to provide hospitals, and the board was more concerned to investigate and control epidemics than to extend the meagre hospital service, though it did try to separate the sick from the healthy in the workhouses.

A quarter of a century later, when the Ministry of Health had replaced the Local Government Board, about half the sick people in workhouses had been transferred to separate hospitals. Exchequer grants were then being made towards maternity, tuberculosis, and other special services; and though there was still no statutory duty to provide hospitals, the Ministry could give a financial stimulus to their construction where it thought fit. The Local Government Act of 1929 brought the poor-law system to an end, and hospitals began to replace workhouses. The medical officer of health was given an important part in the development of the hospital service, and central supervision became less strict as local responsibility increased. General guidance without interference in detail was the policy of the central department.

In 1938 the Emergency Medical Service gave a new responsibility to the Ministry by putting it in direct control of hospitals for the first time. Conceived originally as a means of dealing with air-raid casualties, the service extended its scope when the casualties proved less than had been estimated. The Ministry, spared the expected burden of wounded, turned its hand to organising units for specialised treatment, and concerned itself with such neglected subjects as reablement, the feeding of patients, and nurses' pay.

When the time came for reconstruction, some new organisation of hospital services was needed, if for no other reason than to counteract the financial blows suffered by the voluntary hospitals. The answer finally decided upon was the National Health Service. And so today the central department shouldered the duty of providing a complete health service, over which it exerted, Mr. Pater said, "an irreducible minimum of control." As financier it allowed the hospitals freedom of action within the local expenditure limit—a method which would have been regarded as revolutionary fifty years ago. The hospitals, he thought, had achieved "autonomy with central guidance," and he advised those of his audience who disagreed to think back to the controls of the past.

The Ministry's present functions included promoting the essential minimum in uniformity of method throughout the service; handling and publication of statistics; pleading of the hospitals' case before the Treasury; and preserving a proper balance between the several parts of the health service. In sum, Mr. Pater concluded, the Ministry tried to act as partner to the man on the spot.

Mr. S. C. Merivale (Bristol) said that the detailed changes in methods of budgeting had made life much easier for hospital administrators. Too few administrators realised the boldness and novelty of the partnership between central government and voluntary effort, or the difficulties of reconciling central financial control with maximum freedom at the periphery.

Mr. M. H. Boone (Chesterfield) pleaded for relief from the frustrating delays in hospital building plans.

Mr. L. R. Lorimer (Bradford) suggested that the Minister should include some hospital administrators among the expert advisers on his staff.

The Hospital and its Patients

At a later session, on May 10, Mr. R. M. Titmuss, professor of social administration, London School of Economics, said that the hospital was one of the most complex and intricate units in modern society, demanding "cultivated common sense" in its administration. Three dangers should be guarded against. Firstly, the complex structure, function, and administration might cost more, economically and socially, than was justified by the benefits which the service provided. Organisational fetishes could clog the running of a hospital. Moreover, the more complicated the institution the less critical it became of its own ways; no hospital could remain healthy without self-criticism. Secondly, aims might be obscured by preoccupation with means; boards of governors and hospital management committees tended to devote more time to details of administration than to the essential needs of the patient. Thirdly, the patient might no longer be treated as a human being. The multiplication of scientific and technological advances meant that the patient met more and more people in the course of his investigation and treatment—and this at a time when sickness made him less able to cope with the stress of such encounters. But in the end he was often left in doubt or ignorance about his illness. "The discourtesies of science" set up a barrier of silence which led to misunderstanding and fear. "Nobody told me anything. Nobody asked me. I don't know." Such remarks all too often reflected the patient's distress and confusion on leaving hospital. But doctors and nurses were not callous; the silence which so alarmed the patient was, Professor Titmuss thought, the result of some failure of their professional upbringing; their intuitive simpleness had been overridden by long courses of training which had tended to separate the patient from his disease. A hundred years ago Florence Nightingale had appreciated how reluctant patients were to ask questions and how they could suffer as much mentally as physically; but the mistake of telling them nothing was still being made, and the therapeutic value of courtesy was forgotten.

The quality of medical care was in part an administrative matter. Professor Titmuss thought that the fundamental need was still to decide why one hospital was better than another, just as it had been at the time of the Crimean War. Florence Nightingale had said that the first requirement of a good hospital was that it should do the patient no harm. That this criterion must still be applied was apparent from a recent report on cross-infection in hospital wards, which showed that proven methods of preventing infection were being neglected and misused with harmful results.[1]

Mr. J. A. Tunstall (Cardiff) said that he would add to the discourtesies of science that of noise, which was a constant trial to patients in many hospitals. He agreed with Professor Titmuss that the patient was often refused the courtesy of being treated as an ordinarily intelligent person.

Mr. S. F. Barry (Cardiff) thought that when a patient entered hospital a certain faith in his advisers could be assumed; and elaborate day-to-day explanations of his condition were unnecessary.

Mr. S. Hodkinson (Rochdale) said that the ward sister was the person best fitted to advise on the welfare of the patient. Sisters with whom he had discussed the matter had attributed some of their difficulties to the lowering of nursing standards caused by the expansion of the profession, and to the increasing tempo of ward life with five or six rounds a day by different consultants.

PROPOSED REGISTER OF OPTICIANS

The Interdepartmental Committee which, under the chairmanship of Lord Crook, has been considering whether a statutory register of opticians should be set up, has now reported.[1] The committee is in favour of such a register and proposes that a General Optical Council should be set up with the responsibility of running it.

The new council, the report suggests, should consist of an independent chairman and 20 members, of whom at least 5 would be doctors.

The register should in the first instance be kept in three parts: the first part for opticians who both test sight and dispense glasses; the second for dispensing opticians; and the third for opticians who only test sight and prescribe glasses. The committee hopes that eventually all opticians will choose either to test sight or to dispense glasses, and it thinks that the ultimate aim of the council should be to close the first register.

The 6835 ophthalmic opticians and 755 dispensing opticians who have been approved to take part in the National Health Service would be eligible for registration. Other applicants should hold a recognised qualification and give evidence of having had recent practical experience. The committee proposes not only that the titles "ophthalmic optician" or "dispensing optician" should be reserved for those on the new register, but that no unregistered person should be allowed to practise at all. This prohibition is partly aimed at "indiscriminate sale of spectacles or spectacle lenses in chain stores," and would of course not apply to doctors. In this stringent exclusion the proposed legislation would follow the pattern of the Dental rather than the Medical Acts.

Like the other professional councils the G.O.C. would also be responsible for standards of professional training. Consideration of these functions brought the committee up against some problems. Though much has been done to improve the optician's training, it did not feel entirely satisfied with the standard. Further improvement will probably best be achieved by a coördinating body, such as the new council, with powers of visitation, inspection, criticism, and enforcement. The committee was especially perturbed that the student optician has so limited an opportunity of seeing abnormal conditions of the eye—students have no access to the eye departments of hospitals. The teaching hospitals are fully occupied with medical students, but the committee suggests that the non-teaching hospitals might be willing to help. Medical opinion is clearly uncertain how far the study of these conditions can usefully be included in an optician's training. Medical men who gave evidence agreed that opticians should know as much as possible about the recognition of ocular abnormalities, but urged that it was not in the public interest that opticians should be statutorily recognised as being able to detect abnormalities.

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[1] Goodall, J. W. D. *Lancet*, April 19, 1952, p. 807.

[1] Cmd. 8531. H.M. Stationery Office. Pp. 35. 1s. 3d. The medical members of the committee were: Mr. G. W. Black, Dr. Macdonald Critchley, Sir Charles Lovatt Evans, F.R.S., Dr. John Marshall, and Mr. O. Gayer Morgan.

The problem of what registration should imply also came up when the committee considered the practice of orthoptics and the fitting of contact lenses. In the face of somewhat inconclusive evidence it proposed that the new council should register approved diplomas in these specialities as postgraduate qualifications. Medical and optician witnesses also disagreed whether opticians should use drugs in refraction. In the medical view there is a possible danger of precipitating glaucoma by the injudicious use of mydriatics. The committee cautiously suggests that only opticians who satisfy the G.O.C. that they are competent to use drugs should be allowed to do so; and it further recommends that as one of its first tasks the new council, in consultation with the health departments, should draw up a list of the drugs that opticians may use.

The committee point out that the best way to secure healthy coöperation is to make clear to the public how the responsibility for the care of their eyes is shared by ophthalmologist, general practitioner, ophthalmic optician, and dispensing optician.

PREVENTION OF WAR

A CONFERENCE organised by the Medical Association for the Prevention of War was held in London on May 10 and 11.

MISUSE OF SCIENCE

Prof. F. G. **GREGORY**, F.R.S., spoke of the responsibilities of the scientist faced with the increasing adaptation of his work for the purposes of war. It was no longer possible for the scientist to be content with the pursuit of knowledge, leaving its application to others. The barriers which were springing up everywhere, preventing free access to scientific ideas and information, were a serious menace to the scientific temper. The growing demand for secrecy from official quarters was a threat to scientific advance, and was responsible for the increasing suspicion and hostility of the public towards science and scientists. At all costs the universities should oppose secrecy in scientific work. Scientists had the best of reasons for objecting to the application of science to warfare and preparations for warfare. Such work was highly unproductive, thankless, and fruitless: in a word it was inefficient and hence opposed to the highest objects of scientific endeavour.

BIOLOGICAL WARFARE

Dr. J. H. **HUMPHREY** pointed out that it was impossible to draw any hard-and-fast line between offensive and defensive preparations for bacteriological warfare, or even between work which was specifically war work and that which was part of the general pursuit of scientific and public-health problems. Discoveries which were made for the purpose of conquering human disease could be adapted to spread disease.

Dr. M. R. **POLLOCK** felt that the problem of bacteriological warfare was an ethical one. It involved the perversion of medical science, which in the past had been used only for the relief of suffering. He outlined the proposals embodied in a resolution adopted by the Fourth International Congress of Microbiology at Copenhagen in 1947; this called on medical men and women to abstain from taking part in developing bacteriological technique as a weapon of war, to open all microbiological research institutes to international inspection, and to abrogate secrecy in the publication of such research.

PSYCHOLOGY OF WAR PREPARATION

Mr. J. C. **FLUGEL**, D.SC., suggested that it was the responsibility of the medical profession to make the facts of war psychology more widely known—for instance, the merging of the individual conscience into the collective conscience, and the search for scapegoats. Doctors should protest on ethical grounds about the use of medical knowledge for purposes of destruction. It was necessary that national loyalties should be superseded by world-wide loyalties, so that nations could coöperate in solving the vast global problems of malnutrition, overcrowding, and the control of epidemic disease.

Prof. L. S. **PENROSE** examined the question of how far war was a pathological phenomenon. War was a complicated mental disturbance affecting communities: since it was a disease it should be studied and treated as such. To the individual, on the other hand, war might bring certain advantages; part of the task facing us was to provide peace-time equivalents for these.

Dr. **ALEX COMFORT** held that war was one of the few activities today that instilled a sense of common purpose. Individual values became perverted, so that atrocities which no-one would normally think of performing became permissible when done on the orders of some higher authority. Mass executions and the like probably originated as fantasies in the minds of a few people in positions of command.

Dr. B. H. **KIRMAN** spoke of the danger to children and young people of the conditioning effect of lurid films and comic papers. Large numbers of people in this and other countries were being conditioned for war by media for so-called entertainment.

Dr. **MILDRED CREAK**, while agreeing that the incidence of neurosis in adults diminished in war-time, felt that the impact of war on young children was at the very least confusing and perplexing. We had yet to see what sort of parents those who were children in the late war would develop into. On the other hand, peace imposed disciplines no less than war.

THE DOCTOR'S PART

In the final session Dr. **DUNCAN LEYS** discussed the ethical basis of the recent Declaration of Geneva, and contrasted it with the Hippocratic Oath. Among the objects of the association were the following: to oppose the use of medical science for any purpose other than the preservation of life and the relief of suffering; and to urge that energy and money spent in preparation for war should be directed into the fight against disease and malnutrition. The Geneva Declaration stated: "I will not permit considerations of nationality, race, party politics or social standing to intervene between my duty and my patient." This was an immensely valuable addition to the traditional medical ethic. But the great pioneers of social medicine realised that it was no longer sufficient for a doctor to take a purely personal and individual view of his obligation to society. There was nothing in the Declaration to indicate that doctors must look beyond the individual patient and his immediate illness, and must work to create the conditions of civilisation which alone can create health. Evils which attacked civilisation from within were as much the cause of injury, death, and disease as bacteria and cancer. The ethical principles of medicine should be re-stated in such a way as to proclaim the doctor's duty to think and act in terms of social as well as of individual needs, and when this was done it would be evident that war and the preparation for war were as directly the concern of the medical profession as the control of tuberculosis or the elimination of the diseases of deprivation.

In England Now

A Running Commentary by Peripatetic Correspondents

IN the amusing and widely read strip cartoon that advertises a well-known food drink, the doctors up to now have made their snap diagnoses and uttered their pompous pronouncements on treatment in the privacy of their consulting-rooms. But lately their neurotic patients have started harassing them with recitals of their troubles in unsuitable and inconvenient places. The Rev. Stephen (who had such regrettable trouble with the Church Hall) *may* have met the doctor quite by chance at the lych-gate of the church and blurted out his story spontaneously. But, when Sir Adam finds Lady Helen weeping in the oak-panelled drawing-room of the Manor House, does she remark casually, "I must consult Sir Gregory in Harley Street on Friday, when I've got a date at the hairdresser's." Not a bit. She says, "I'll try and have a word with the doctor at the meet tomorrow." What's more, she does; and instead of yelling a polite "Tantivy!" or "Yoicks!" and setting spurs to his horse, he weakly allows himself to be drawn into listening to a dreary recital of symptoms, lasting for at least two fields. I cannot help viewing these churchyard and covert-side consultations with grave misgivings.

* * *

Nowadays by the time a man qualifies he more often than not has already made up his mind to "go in for" surgery, eyes, gynæcology, or what not. But this was not always so; it used to be the exception. When I was very young our teachers took it for granted that we would go into general practice first of all. They told us how important it was to take an interest in our patients. We should follow them up, read up their cases, and cultivate one or other branch of the profession in our spare time. Then, if we were *very* good boys, we might in time reap our reward and become *Specialists.*

Always of a credulous disposition, I did my dutiful best to follow this advice when I went into practice. It went against the grain, because I had my own ideas on how to spend spare time. Perhaps I pretended to be keener than I really was. I had done that before in several house-appointments, assuming a bogus enthusiasm to many too-soon-to-be-disappointed chiefs. I think they liked me all right; but they obviously didn't think much of my abilities as a house-officer. How right they were!

In general practice I conscientiously followed my surgical cases to hospital, soon becoming a familiar and dreaded foreign body in the operating-theatre. My appearance was an alarm signal for a phalanx of hooded probationers to execute a cutting-out movement and separate me from the table. For I took my visit seriously and thought I ought to see inside the patient.

I also bought many expensive instruments, designed to bring into view those intimate parts of the body not usually open to inspection. Among my country patients these instruments earned me a reputation for eccentricity and sometimes excessive curiosity. For those were the days when feeling the pulse and inspecting the tongue was held to be a sufficient examination for most purposes. Slowly it became clear that seeing bladder trigones, vocal cords, and eustachian tubes gave me only the mildest of thrills. I seemed no nearer being a specialist, though I had been a *very* good boy and done all my teachers had told me. But did I *want* to specialise in anything? No, of course not. I didn't want to do anything at all, except gratify my natural indolence by practising medicine from the depths of a well-upholstered consulting-room chair, where I could listen in comfort to the stories people told me.

I liked being told stories, and I must have listened very well; for the people came back and sent their friends. They said I had helped them tremendously and I was wonderful. Nobody ever said that when I had looked at their trigones or their cords, or blown into their tubes. I found I was most wonderful when I sat quite still and did not say a word.

Then I moved to London and sat and listened there. And I was still wonderful. What's more, I still liked hearing the queer lurid stories these people told me, so I started reading about them; and after many years my teachers turned out to be right after all. I am not exactly a specialist in psychology; but I am a few steps on the way. If I keep on being good, and if I live long enough, I may be one in my old age. Anyway, sitting and listening, or even reading, will be much better fun than golf or growing cabbages—and will pay better.

All this should point a moral; something valiant and inspiring, like *nil desperandum.* But it wouldn't be true. It was just an accident that could happen to anyone. You never can tell. Ah! There's the moral, if there must be one. *You never can tell!*

* * *

"Getting a little thin on top, sir." "*H'm.*" "Scalp's a bit—er—dry, sir." "*Oh.*" "Rather more dandruff than I like to see myself, sir." "*H'm.*" "Ever tried anything for it, sir?" "*Pretty well everything.*" "Really, sir? Have you tried 'Scalpo'? Excellent stuff. We all use it ourselves here, sir." "*H'm.*" "If I might ask, sir, I'd be interested to know what you have used." "*Usual things. Sulphur, salicylic acid, resorcinol, 'Ex,' 'Wy,' and 'Zed'; none of them made the slightest difference.*" "Ah yes, of course, sir. I'd forgotten you're a doctor. Of course! What you want is Doctor James's '*Scientific.*' I believe we still have just one bottle left."

And so on, and so on. I am rather proud of never being really cornered, but I have been driven into taking some pretty unfair expedients. One was to imply that I have a consulting-room in Harley Street—there are still strata of society in which that completely silences any medical argument. But expedients, it seems, will soon be needed no longer; for on the strength of the correspondence in this journal a few months ago I tried cetrimide for seborrhœa, and it worked! The elaborate formulæ of the earlier correspondents are unnecessary: I use the neat powder and follow the instructions on my wife's shampoo packet. I have washed my hair with it now for six months; in that time I have had my hair cut five times by four different barbers, and not one has tried to sell me a thing—the best possible proof of cure.

* * *

We have been using a new seed corn drill this spring, so we have escaped the broken wheels and other mishaps recorded in these columns last year. But fresh horrors have arisen, mainly because the drill is so up to date. A man who rides the board of the average corn drill must be able to stand up, hold on by one hand, and wield an iron hook to remove lumps of turf or trash that get caught up and stop one of the seed pipes running properly; a clout with the said hook usually starts it going again. This new drill needs the constant attention of a mechanical engineer who is also a skilful acrobat. The various self-cleaning devices work admirably, but the cleaners must be kept clean. This involves delving into the bowels of the mechanism and its cog wheels while on the move, the driver having made it clear at the outset that he stops for nothing except more seed. It is just as well that there are no factory inspectors in these parts clamouring for machine guards. But that is not the only snag. The wet spring with its late snow has left some horribly wet patches in the fields, and to wait for them all to dry would mean that nothing would be done; it is mid-April as I write. To prevent the drill getting stuck the man in charge must dismount from time to time and walk briskly behind, still manipulating the lever that controls the depth of drilling, until the soft place has been passed, when he can return to his board. In remounting it is almost impossible to avoid banging one's knee on the projection provided for that purpose.

This well-recognised occupational hazard might well be called "drill knee" and classed with horse-rake leg, which someone described in these columns, and with the bruising of the gluteal region familiar to doctors practising in the Eastern Counties corn lands as "binder bottom" and seen in men who have sat for two days on a reaper-binder in harvest-time.

* * *

News from School.—"In biology we went and found a lot of animals in the school pond, and then told them what they were."

Letters to the Editor

RELAXATION IN LABOUR

SIR,—Many will agree with Mr. Clayton (May 10) on the points he raises about relaxation in labour. Women in labour may nowadays be denied effective relief because they are expected to be satisfied with some "ritual."

Popular demand has made many authorities feel obliged to provide some form of antenatal "class." These classes vary very greatly in content and method. It is possible that some of the instruction given may be valueless; but the authorities in charge feel that honour has been satisfied by providing a class, and that no further effort need be made; so attention to what possibly may be of the greatest value may be neglected.

Before antenatal classes are widely developed, involving heavy public expense, we must try to make a scientific appraisal of what, if any, factors in them really are important. For this reason the undersigned committee, under the presidency of Prof. W. C. W. Nixon, has embarked on a nation-wide survey of forms and results of antenatal "training." We have been offered considerable support, though a few hospitals have felt unable to coöperate. It is important to include a large sample of methods and results of training, owing to the wide variability, as well as a control series.

The investigation is including not only what may be called the "mechanical" factors in labour, which Mr. Clayton mentions, but also the reactions and feelings of the mothers. The field work will be carried out by a reputable body using their own trained interviewers. Information from all sources will be collated and analysed mechanically. The committee will be responsible for producing a report which will be published and made freely available.

We should be glad of suggestions and data from general-practitioner obstetricians and others whom we have not, as yet, been able to contact. Letters should be addressed to Mrs. Williams at 26, Brampton Grove, Hendon, London, N.W.4.

MARJORIE C. JOHNSON
Chairman.
SHILA G. RANSOM
MURIEL B. TIBBETTS.
MARGARET WILLIAMS
Secretary.
D. L. LAMBERTH
Coöpted member.

Research Committee,
Obstetric Physiotherapists' Association.

CORONARY AND MYOCARDIAL DISEASE

SIR,—Dr. Harrison (April 26), in assuming that medical practitioners have ischæmic heart-disease in mind when they certify "myocardial degeneration," &c., to be the cause of death, may himself have succumbed to the temptation, so great nowadays, to blame the coronary arteries for all manner of ills. He is quite possibly correct as regards some of the deaths under 65, or even 70, years of age; but the great majority of certificates of "myocardial degeneration" (or some such wording) refer to people over 70, and I wonder whether his inference is justifiable among these older men and women. The pairs of figures and percentages [1] in the accompanying table are suggestive.

After 80 years of age the contrasts between "coronary" and "myocardial" disease are even more striking. There appears to be more here than mere looseness of terminology. It may be that the older the patient the less careful the practitioner with his certificate, but that would need to be proved. (It is certainly true that with advancing age it becomes less easy to complete certificates accurately and simply.) This unit is now conducting a small inquiry, with the help of the General Register Office and many practitioners in London and the Home Counties, designed to elucidate some of these problems of death certification in cardiovascular disease, "one of the darkest areas of vital statistics" [2]—an area to which the recent and otherwise valuable W.H.O. guide [3] could not pay much attention. What I want to plead for here in particular, though it is incidental to the main purpose of Dr. Logan's interesting paper (April 12) which started this discussion, is some clarification of our notions of "senile" heart-disease.

DEATHS CERTIFIED IN 1949 IN ENGLAND AND WALES

Cause group	Males		Females		Both sexes	
	Under 70	Over 70	Under 70	Over 70	Under 70	Over 70
Diseases of the coronary arteries, angina pectoris. No. 94 ..	16,097 *(58%)*	11,458 *(42%)*	6181 *(40%)*	9186 *(60%)*	22,278 *(52%)*	20,644 *(48%)*
Myocardial degeneration, &c. No. 93c ..	8662 *(23%)*	28,491 *(77%)*	7505 *(16%)*	40,476 *(84%)*	16,167 *(19%)*	68,967 *(81%)*

I have, for instance, recently read three admirable accounts of senile myocardial disease [4–6] or "presbycardia," [4] as an entity distinct from coronary or "ischæmic" disease. Yet it is far commoner to read statements such as: "When it comes to cardiovascular disease in ageing, I do not see how you can get around the fact that whether it is labelled 'disease' or 'ageing,' the common or garden variety of arteriosclerosis is about 99·4 percent of the problem." [7] Is this true? Others, who interpret what is happening rather differently, might counter that "The absence of an obvious etiologic basis for heart disease in an elderly person does not, ipso facto, warrant the diagnosis of arteriosclerotic heart disease." [6] Dr. Heggie (May 3) has referred to various relevant morbid anatomical processes; and clinicians see cases—for example, of congestive failure in elderly persons—that have no obvious cause. Examination of standard British and American textbooks of cardiology, however, shows that there is no clear recognition as yet of any such senile cardiac condition. If, in fact, it exists at all, it may be a common form of heart-disease, in view of the number of elderly persons in the population, and the fact that over half of *all* deaths now take place after 70 years of age.

It is a confession of ignorance to talk of "involutional" changes, and the like. But it must surely be important to settle whether there is an entity of senile myocardial degeneration, in addition to coronary atheroma-thrombosis and its consequences, and which can be lethal by itself or together with other disorders not themselves serious. This is only one instance, of course, of a very general problem—our inexperience among the multiple syndromes of old age. Possibly death certificates, with all their recognised shortcomings, may, as so often before, hold valuable clues. The very different registrations of "coronary" and "myocardial" disease with age may point to different clinical conditions, and to different pathological processes underlying them.

J. N. MORRIS.

Social Medicine Research Unit,
Medical Research Council,
Central Middlesex Hospital,
London, N.W.10.

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[1] Registrar-General's Statistical Review of England and Wales, 1949. Tables. Part I. Medical. H.M. Stationery Office, 1951.

[2] Morris, J. N. *Lancet*, 1951, i, 69.

[3] Medical Certification of Cause of Death. Geneva, 1952.

[4] Dock, W. *N.Y. St. J. Med.* 1945, 45, 983.

[5] Morgan, H. J. *Trans. Ass. Amer. Phys.* 1951, 64, 54.

[6] Harrison, T. R., Resnik, W. H. Principles of Internal Medicine. Edited by T. R. Harrison. London, 1951.

[7] Steele, J. M. Transactions of Thirteenth Conference on Problems of Ageing: Josiah Macy, Jr., Foundation. New York, 1951.

CORTISONE AND CAUTION

SIR,—Your annotation of May 3 makes significant reading to one who as early as June, 1949, was uttering a serious word of caution against too-hasty acceptance of the apparently magical results of cortisone treatment.[1]

The three years which have since elapsed have more than justified this warning. It is now clear beyond doubt that cortisone is purely a symptomatic treatment, and not a causal therapy, its action being solely to suppress the inflammatory response of the organism to the rheumatic noxious agents. This tends to send the patient into a "fool's paradise" while its effect lasts, for it really constitutes no basic attack against the rheumatic process, which is left entirely unaffected. On the other hand, by switching off the alarm-clock of the pain, so to speak, it induces the patient to undertake more activity and use the joints more intensely, thus increasing damage to the cartilage which already probably exists. This accounts *inter alia* for the grave setback so often observed after cortisone treatment. Anyone having had the opportunity to see such grave deterioration after cortisone treatment will agree that the balance, apparently equal between that treatment and the "basic classical treatment," must actually be heavily tipped against cortisone, as the classical treatment presents no such danger at all. The cautious statement by Martin *et al.*[2] that "cortisone is an important adjuvant to the treatment programme of many patients with active rheumatoid arthritis" can only be accepted, in my opinion, if there is added "if applied by a physician with special knowledge and full awareness of all possible pitfalls."

London, W.1. L. SCHMIDT.

DIABETIC ACIDOSIS WITHOUT KETONURIA

SIR,—The sound criticism of my paper made by Dr. Lawrence, Dr. Oakley, and Dr. Martin (May 3) is welcome, because a watertight diagnosis of the case reported had not been made and, as I mentioned, neither plasma carbon dioxide nor blood-ketone determinations were done.

Dr. Lawrence and his colleagues say that similar findings may be made in renal acidosis. This is difficult to refute because the pathology of diabetes and of uræmia may be inextricably mingled when coma supervenes in a diabetic. However, regarding the points raised in their letter concerning the presence or absence of albuminuria and of oliguria or anuria, Dr. Lawrence himself, in the paper[3] which, I regret, I omitted in my review of the literature, pointed out that albuminuria is the rule in diabetic coma, and that not only may oliguria or anuria be present, but also urinary casts and a raised blood-urea. Therefore even if all these were present the diagnosis of diabetic acidosis would not necessarily be invalidated, whilst their absence would make it a more likely diagnosis than renal acidosis. I may add that in the case recorded there was no oliguria or anuria; had there been it would of course have been reported.

When there is difficulty in making a differential diagnosis, one must take all the available evidence into consideration. The history of a case is often the most important factor, and here it is of overwhelming significance. It is that of typical diabetes of recent origin, severe in degree, and rapidly leading to coma; and when one adds the presence of heavy glycosuria, considerable hyperglycæmia, and acetone in the breath, I feel there can be no doubt that the true diagnosis is diabetic acidosis.

Finally I must point out that if a patient is suffering from diabetic acidosis without ketonuria (I did not state or infer "without ketonæmia"), and is not treated urgently with adequate doses of insulin, then it will soon be too late to discover an underlying ætiology, if indeed any exists.

Royal Victoria Hospital,
Bournemouth. JACK HENNEMAN.

WHAT SHOULD THE NURSE BE TAUGHT?

SIR,—Mr. Hodkinson (May 3) agrees with other correspondents that young girls employed in hospitals should not perform nursing duties. Can he suggest any alternative likely to be acceptable to them by which they may earn the wages provided by the taxpayers?

Hove. C. M. OTTLEY.

PRISCOL IN OBSTETRICS

SIR,—In your issue of March 22, Mr. Farquhar and Mr. Mills, commenting on my suggestion that 'Priscol' might be of value in obstetrics,[1] record their findings in a small number of cases, confirming a possible oxytocic action. Since my original communication, a preliminary study has been undertaken to assess the value of the drug in the treatment of various conditions associated with pregnancy.

This series comprised 16 women in the second and third trimesters, 43 selected either for induction of labour or during labour, and 30 in the postpartum period. The dosage employed was somewhat different, with an initial oral dose of 50 mg., followed after one hour by an intravenous dose of 50 mg. which was repeated after a further hour. It was found that only the intravenous route gave a satisfactory response. The initial oral dose did not evoke any uterine response, but was given to prolong the duration of action of the intravenous material. When given by mouth in doses exceeding 50 mg. four-hourly, nausea and vomiting resulted, so presumably a sufficiently high blood level cannot be achieved by this route alone. A test dose, as recommended by various workers, was not given since the women in this group showed a consistent freedom from any but the most mild side-effects.

The results in the induction of labour were variable. In 2 women, judged to be normal and at term, the response was satisfactory. 2 similar cases were given stilbœstrol 30 mg. followed by priscol, with a prompt response accompanied by the undesirable features of contractions more painful than those experienced in previous labours although normal in their duration, polarity, and relaxation phase, and by partial suppression of lactation. Another 3 similar cases showed a good initial response which diminished after about twelve hours, to become refractory to further doses. No response was obtained in 1 case with premature rupture of the membranes. A very good response was seen in a girl with chronic hydramnios who had not responded to attempts at medical and surgical induction. An 8-para, known to have suffered for two years from diabetes mellitus treated by dietary control only, again showed an excellent response.

Whereas her previous labours had all lasted approximately forty-eight hours, her present one was shortened to twelve hours. During labour and for twenty-four hours afterwards she showed signs of mild hypoglycæmia, followed by a complete absence of reducing substances from the urine during the puerperium despite the fact that before admission a brick-red deposit had been obtained with Benedict's reagent. Other workers have commented on hypoglycæmia following priscol in diabetics under treatment for peripheral vascular disease.

In patients subject to toxæmia of pregnancy a remarkably good oxytocic effect was observed, but only after intravenous or very much larger intramuscular administration. In 3 cases with signs of pre-eclamptic toxæmia, oral doses produced within twelve hours a release of retinal vasospasm, diuresis with diminution of œdema and lessened albuminuria, and relief of accompanying gastro-intestinal symptoms and of headache, but no stimulation of the uterus. 1 eclamptic was treated with priscol.

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1. Schmidt, L. *Brit. med. J.* 1949, i, 1004.
2. Martin, G. M., Polley, H. F., Anderson, T. P. *J. Amer. med. Ass.* 1952, 148, 525.
3. McCance, R. A., Lawrence, R. D. *Quart. J. med.* 1935, 4, 53.

1. *Lancet*, 1951, i, 802.

She had had two fits on the day of admission and a third on dmission; her blood-pressure was 210/160 mm. Hg, with ery gross œdema, disorientation, and hyperirritability. hree half-hourly doses of 50 mg. intramuscularly were iven, labour commencing after the third. Although none of he usual sedative and anticonvulsant measures were employed, o further convulsions resulted. The drug was given during he puerperium following the rapid delivery of a normal child. Profuse diuresis commenced about thirty hours after delivery, ollowing the initial profound oliguria. By the seventh day ost partum, physical examination was entirely normal.

During labour the drug was tried in primary uterine nertia with unsatisfactory results. Of 20 cases of econdary uterine inertia 18 were controlled after the irst or second intravenous dose (oral dose omitted). The further labour had progressed, the more certain the esult; thus in the second stage at least 6 cases were delivered after a single dose of priscol where the inertia, otherwise uncomplicated by mechanical factors, would have warranted assistance with forceps.

3 cases of accidental hæmorrhage were treated with priscol. Regular expulsive uterine contractions followed n all after a single intravenous dose; colicky contractions and persistent uterine tenderness decreased; and, paradoxically, the bleeding diminished, as judged by the patient's condition, the height of the uterine fundus, the vaginal loss, and small amount of fresh clot expelled with the placenta.

In postpartum hæmorrhage, the rapid strong response required of oxytocics was not found in priscol.

Certain peculiarities of the drug's action on the uterus became apparent in this series. Firstly, by whatever route it was given, a state was produced closely resembling that described as Braxton-Hicks contractions. For the purpose of this survey, such was not taken to be a true oxytocic response. Induced uterine contractions were regular, strong, not unusually painful, and punctuated by phases of complete relaxation. Immediately after an intravenous dose the phases of systole and diastole were often equal, lasting one and a half minutes each, and later becoming more widely spaced; duration of action was from two to four hours. Continuous uterine spasm never occurred, and good relaxation of the cervix was usual. The longest single contraction recorded after injection was two and a half minutes. With an "overdose," contractions previously induced by priscol were found to decrease. The hypodermic administration of atropine gr. $^1/_{100}$ generally stopped priscol-induced contractions.

At no time during this investigation was the drug found to be harmful to the mother, nor did careful watch reveal that the fœtus had in any way suffered. Even in the toxæmic patients the effect on the blood-pressure was negligible, not amounting to more than a transient fall of 10–15 mm. Hg systolic after intravenous administration. These and other side-reactions, such as "priscol shock," were conspicuously absent in the antenatal and intrapartum patients, although it was found that such patients might show such alarming reactions as tachycardia, giddiness, and hypotension, in a circumscribed period of approximately six to twenty-four hours post partum.

In the application of priscol as an oxytocic in pregnancy, this investigation has revealed certain defined properties. Whilst not having the same constancy and strength of action of other oxytocics, it possesses the advantages of safety for both mother and child in doses that have ranged between 10 and 250 mg. in twenty-four hours. The most satisfactory application as an oxytocic is probably in toxæmia and in secondary uterine inertia. In the treatment of pregnancy toxæmia the drug relieves some of the abnormal signs, but lacks a hypotensive effect. (Here it may be noted that a patient who has received oral treatment for approximately seven days will not exhibit any oxytocic response.) Those women who received oral doses in the second and third trimesters did not abort.

I wish to thank Dr. D. P. de Villiers, honorary medical superintendent of St. Monica's Maternity Home, Cape Town, for his approval, interest, and assistance.

Stellenbosch, Cape Province,
South Africa.

P. A. FOSTER.

INCOMPATIBLE TRANSFUSIONS

SIR,—Dr. Discombe in his article (April 12) very kindly thanks us for having "read successive drafts of this paper and given me the most valuable criticism and advice." A number of pathologists concerned with blood-transfusion have, in our opinion quite unjustifiably, read this as meaning that we endorse in detail the methods of blood-grouping and direct matching recommended and used by Dr. Discombe. While we believe that in his highly experienced hands these methods give reliable results, they are not those which we ourselves use; nor do we recommend them for general use. The methods which we use and recommend are those described in the official memorandum of the Medical Research Council.[1] These include (p. 59) suggested methods for dealing with extremely urgent cases such as those to meet which Dr. Discombe's procedure was designed.

We do, however, regard Dr. Discombe's paper as a valuable record and warning of some of the ways in which incompatible transfusion may occur, and we should like to support his suggestion that the passage of blood from hand to hand should be checked as is that of dangerous drugs.

Blood Group Reference Laboratory,
Lister Institute, London, S.W.1.

A. E. MOURANT

DOROTHY M. PARKIN.

Lister Institute, Elstree.

W. d'A. MAYCOCK.

SYNERGY OF HEALTH AND EDUCATION

SIR,—The happily chosen title of your leader of May 10 conjures up a picture of lively energy, combining the best features of Hygieia and of Pallas Athene, taking mortal shape through Local Administration. This so exactly fits my own conception of the School Health Service that I can only wish I had thought of it myself —a poor but sincere tribute.

Alas! there are few positive tributes to the existing service in what follows, though more will emerge from the full proceedings of the Margate Congress, when these appear in the *Journal of the Royal Sanitary Institute*. The annual reports of the Chief Medical Officer of the Ministry of Education (*Health of the School Child*), which you quote, provide a continuous record not only of purpose but also of achievement, extending back to the days before the Board of Education became a Ministry. The change in title of the School Medical Service to School Health Service in 1944 signalised a swing from a negative to a positive view of health which has not always been implemented or even understood.

Your leader brings out the widely held view that the service is not doing so badly if it avoids redundancy, which means that it does not relieve (or rob) the busy practitioner of too much of the time-consuming diagnosis and treatment of minor maladies. You do not mention the school health officer's responsibility in the intellectual and emotional, as well as physical, growth of the scholar —both as child and adolescent—or his work with the educationally and physically subnormal.

I appreciate your kindly reference to the series of "Twenty Questions," published last year, with the twenty answers, in the *Medical Officer*. Two points made at the very beginning and end of this series deserve special mention. It was suggested that such a preliminary questionary would enable experienced school health officers to codify their own conceptions of what they were supposed to be doing: then, having positively

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1. Mollison, P. L., Mourant, A. E., Race, R. R. The Rh Blood Groups and their Clinical Effects. Medical Research Council memorandum no. 27. H.M. Stationery Office, 1952.

pin-pointed, present and past, they might project a beam that would tell them the direction in which their future must lie. This Cinderella (with apologies to all the others), at 50, is no chicken; and having discouraged the more possessive forms of pædiatricianism so long she should stand a good chance of another 50 years of blessed singleness. Her prototype, however, did rather well for herself by going all out for a suitable consort.

XX.Q.

JOINT-STRAIN IN SLEEP

SIR,—As a lay member of the public, and one of the "thousands of Londoners" who fire-watched in Central London, I should be interested indeed to have some further explanation of Dr. Pai's statement (May 3) that there is no evidence to prove that painful disabilities have resulted from sleeping in uncomfortable positions during the war years.

First, most of us slept, when opportunity offered, out of sheer exhaustion; and in some cases we may not have been lying any more incorrectly than had we been at home. How many people know anything at all about "sleep posture"? But where acute discomfort was experienced—as in the case mentioned of armchairs for the elderly—may there not still be quite a number of people walking around with slight, but unrecognised, disabilities arising from that cause? Unless those people happen to get ill, what are the chances of their disabilities being detected, the origin traced, and the results recorded in the "clinical and statistical" evidence of which Dr. Pai can find no trace?

London, S.W.1. JANET BURTON.

RESTRICTIONS IN HEART-DISEASE

SIR,—In his Lumleian lectures for 1951 Sir Adolphe Abrahams[1] effectively disposed of the notion that severe exercise can harm a normal heart, and also reminded us that even in the presence of established valvular disease there may be no physical incapacity provided that the myocardium is healthy. Both he and Levy[2] have emphasised that many of the restrictions applied to patients with valvular disease are completely unnecessary, and your leading article of April 26 again draws welcome attention to the danger of what Dr. William Evans has called "unwarranted cardiac invalidism."

Whilst it is a sound principle that "the patient himself is the best judge of what unduly strains his circulation," it is perhaps insufficiently appreciated how high the dyspnœa threshold may be raised by physical fitness with its resultant economy in cardiac function. The following case-record illustrates this point.

The patient was a symptomless man, aged 24, in whom valvular disease had been diagnosed at the age of 8. All games had been forbidden, but he had later taken up cycle-racing and was anxious to continue the sport. The physical signs were those of aortic incompetence, aortic stenosis, and mitral stenosis with sinus rhythm. Radiologically the changes in heart contour were early but unequivocal, and suggested that the aortic lesion was predominant. Further inquiry elicited that he always cycled 16 miles daily to work and up to 100 miles at most weekends with a club. Furthermore, he had recently won a 25-mile cycle race and soon afterwards had completed without distress a Continental tour of 1000 miles which included the French Alps. When questioned about his physical endurance he remarked: "I'm as good as the next at the end of the day."

Whilst physical fitness is even more desirable in patients with valvular disease than in healthy people, two uncertain factors continue to call for some restraint when an attempt is made in each case to define the upper limit of physical activity. The first of these is the difficulty of judging whether rheumatic carditis is completely inactive or smouldering on—and unfortunately this often applies to just those young patients who most commonly seek guidance. Probably the best method at present is careful clinical and radiological assessment of doubtful cases over a period of several months before a decision is made. The second factor is the theoretical possibility that habitual strenuous exercise, though remaining for several years within the capacity of an athletic subject with inactive rheumatic heart-disease, may yet ultimately induce premature cardiac enlargement and heart-failure.

It seems that, whilst the patient is usually the best judge of what he can comfortably do after exercise tolerance has been raised by graduated exercise, there remains a group of persons similar to the one I have described for whom the decision must be made by the physician.

London, W.1. ROBERT BENSON.

GREEK TO THE PATIENT

σιρ,—εἰ ὑος ἰντερεστεδ τε͡υ ρι͡εδ μιστερ ἀσ́ερσον'ς λεττερ ἰν εὑρ ἰσ́ε͡υ ὀφ ἠπριλ 26 0, ἀς εἰ με͡ισελφ φρι͡εκυ͡εντλι εὑς γρι͡εκ ἱερωγλιφικς ἀνδ ἰνγλις́ ὑερδς φορ νωτς ἰντενδεδ ὠνλι φορ μει ὠν εὑς. θα͡ιρ ἀρ ὀφ κορς ἀ νυμβερ ὀφ λεττερς ἀνδ σο͡υνδς ὑιχ ἀφ νω γρι͡εκ ἐκυ͡ιφελεντ, βυτ φορ θι͡ες εἰ εὑς ὑοτ δεφε͡ισες εἰ θινκ φιτ; ὀρλθω θη μη νοτ βι͡ε ρεδιλι ἰντελεγεβελ τε͡υ ἐνιβοδι ἐλς, ἀνδ ὑυδ προβαβλι κορς κονσιδεραβελ διστρες τε͡υ θε μορ πεδαντικ ὀφ ἑλενιχ σχολορς.

εἰ δο͡υτ ὑεθερ θις σιστεμ ἰς ὀφ μυχ φαλ͡ευ τε͡υ μεδισιν, ἀπ̂αρτ φρομ θε εὑς μιστερ ἀσ́ερσον μενσ́ονς, ὑνλες περάπς ἰτ κυδ βι͡ε μηδ τε͡υ δισκυρηγ́ θε πρεσεντ, ὑνφορτε͡υνητλι φλυρισ́ινγ, στητ ὀφ ἀφα͡ιρς ὑα͡ιρβε͡ι μωστ μεδικαλ πρακτισ́ονερς' νολήγ ὀφ γρι͡εκ ἰς λιμιτεδ βε͡ι θα͡ιρ νολήγ ὀφ φισικαλ φορμε͡υλα͡ε ἀνδ θα͡ιρ σκιλ ἰν ἐση ρε͡ιτινγ.

The University Union,
Manchester.

GERALD SOLOMON.

HICCUP DURING ANÆSTHESIA

SIR,—The experience described here may throw some light on the origin of this symptom.

Whilst I was pulling on the stomach in the process of performing vagotomy the patient developed persistent hiccup. After the anterior vagus nerve was cut the hiccup was still at full throttle. As I cut the posterior vagus nerve the effect on the hiccup was immediate. The ensuing calm and silence were so impressive that I was prompted to make a wild suggestion to my anæsthetist, Dr. F. K. Boston, that here might be a new remedy for the distressed inebriate. Further traction on the stomach was necessary for a few minutes, but there was no more hiccup. There had been no immediate alteration in the anæsthesia.

I have since seen the patient in the outpatient department, and he says that he is not aware of having had so much as a single hiccup since his operation.

Perhaps it was coincidence; on the other hand, perhaps others have made this observation or may yet make it. Dr. Boston tells me that the anæsthetic agents were spinal 'Nupercaine,' thiopentone, nitrous oxide and initially enough 'Flaxedil' to allow satisfactory introduction of an endotracheal tube.

I am diffident to comment on a subject about which my knowledge is mainly that acquired by all of those occasionally afflicted; but the greater frequency of hiccup in light anæsthesia, especially when the œsophagus or stomach are pulled on, has been noted by several of your correspondents, and I also share their view that with the advent of "relaxants" the target of upper abdominal surgery has changed from steady resistance to jerky flaccidity.

Perhaps this observation may add a prop to the contention of Dr. Rollason (March 29) that "It is my pression that the afferent path of the hiccup reflex is n the vagus, and the combined vagolytic effects of xedil, pethidine, and hexamethonium prevent its currence." Dr. McGill[1] has reported dramatic response a patient with intractable hiccup to hexamethonium —which may be a vagal hint from a conscious subject.

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[1] *Lancet*, 1951, i, 1133, 1187.
[2] Levy, R. L. *Circulation*, 1952, 5, 454.

Radcliffe Infirmary, Oxford. G. E. MOLONEY.

ARTERIAL GRAFTS

SIR,—Even the concept of what is "living" is elastic nd ill-defined. In an annotation[2] you state that arterial rafts "die" and become inert tubes which are soon ined by intima from the host. You add that important lastic fibres persist and that the graft functions perfectly.

In 1949, in collaboration with Dr. O. Croxatto,[3] I studied in dogs thoracic aortas that had been grafted for more than one year; and we concluded that part of the graft could be considered "alive." Our main reason for this conclusion was that the elastic layer had degenerated only in the external third, while in the zones that were near the lumen of the aorta, from which the necessary elements had diffused, the elastic tissue retained its normal characteristics. Furthermore, isolated foci of necrosis were observed which made the normal aspect of the rest of the graft more noticeable.

Naturally elastic fibres are not "living" cells; but, being susceptible to degeneration and necrosis, their normal appearance one year after the operation justified the assumption that the graft was not "dead."

In respect of the fate of cellular grafts, we have found that in homografted dog lungs, epithelial cells were well preserved 20 days after grafting. We were unable to obtain survival for more than 24 days.[4]

Buenos Aires, Argentine. ALFREDO LANARI.

POST-STARVATION GYNÆCOMASTIA

SIR,—In connection with your annotation of March 22, I should like to mention that during the occupation of Greece by the Italians in 1942–43 I was held as prisoner; and, since I served as a physician to the prisoners, I observed several cases of gynæcomastia in younger people when the food ration was improved in 1943.

The patients presented the clinical features described by Musselman[5]—"disc-like swellings in the subareolar breast-tissue." I classified this as gynæcomastia of "re-adolescent" type.

You rightly accept "post-starvation gynæcomastia" as a distinct entity, and the explanation of it may be as follows:

> During starvation activity of the hypophysis-testis axis diminishes owing to lack of proper amino-acids and/or vitamins (B complex, E). When these factors are again supplied the activity of the endocrine system, and especially the hypophysis, increases, with augmented secretion of gonadotropin and prolactin, causing the same effect as in adolescence. There is firstly stimulation of the breast-tissue with gynæcomastia, and secondly stimulation of the testis with increased production of androgens. This increase of androgens inhibits hormonal secretion by the hypophysis and restores normal function of the hypophysis-testis axis. This probably causes the disappearance of the gynæcomastia; but we also have to consider the fact that androgens have a direct effect on the breast-tissue.

This opinion is supported by another clinical observation: that starvation was the main cause of secondary amenorrhœa in many women (previously with normal menstruation) during the starvation of occupied countries, and especially in Athens. Improvement of the food ration restored normal menses in all these women without any special hormonal treatment.

Toronto, Ontario, Canada. L. G. POLYMENAKOS.

VARICOSE ULCERS

SIR,—Your annotation of April 5 is both timely and wise. This neglected scrap-heap of surgery deserves more attention. Varicose ulceration causes much physical suffering and ill health, very much incapacity, and a very great economic loss of working hours—probably far more than fractures. Nevertheless fractures have rightly now acquired special departments and specialised orthopædic treatment, thanks largely to Watson-Jones and McMurray. But the poor ulcer is still haphazardly dealt with by whomsoever cares to deal with it—newly qualified house-surgeon, registrar, surgeon, dermatologist.

A regular clinic is vitally required in each centre—in charge of someone gifted with enlightened enthusiasm who will study the whole gamut of varicose conditions, and who will see to it that his staff of assistants and sisters and nurses are not for ever changing. There is no one cure for any type of ulcer. Each case must be studied. The director of the clinic will cure nearly all cases by means of the varied techniques, "dodges," remedies, and methods born of his experience.

The real and only problem is the waterlogged dropsical leg. Firm compressive bandaging of some kind or another, applied with the proper technique, is the answer to nearly all cases. Once cured (or healed) those legs need support always—either bandage or stocking. I tell the *old* ladies that their legs also need their own special supportive corsets—even as their bulging abdomens permanently need their own type of corset. The longer that I work in my clinic with its 100 cases weekly—I have done this now for twenty-five years—the more do I realise the truth of the foregoing statements; and the more do I realise that surgery is not very often indicated.

The prevention of ulceration consists only very partially in dealing with varicose veins—because most cases of superficial varicosities do not lead on to ulceration. Mr. Partridge (April 19) raises one important point—about deep-seated varicosity and deep-seated thrombi altering the course of circulation. Real prevention lies in the maintenance of good health—preventing obesity, avoiding tight garters, lessening the hours of standing, attending to women's correct footwear, &c. This, surely, is the opportunity for us all alike—the family medical adviser, the houseman, the physician, and the surgeon, who should always also be a good physician.

Liverpool. STUART MCAUSLAND.

SIR,—I have read with interest your annotation and the subsequent correspondence. I would strongly endorse the need for a combined dermatological and surgical approach to this problem, and would go further and plead for a general consideration of the patient as well as his visible local lesion.

My interest in this condition has been stimulated by investigations that I have been making into the amino-acid content of the exudate of crural ulcers, following up German work on the effect of glycocoll on the healing of ulcerated surfaces.[1] I have found that the amino-acid content of the exudate from a varicose ulcer is very different from that of normal serum. As the ulcer heals the amino-acid pattern approaches that of normal serum. By applying a suitable dressing containing amino-acids the ulcer can be made to heal in a few weeks—but unless the underlying cause is eliminated, the ulcer will relapse.

London, W.1. DAVID HALER.

SIR,—From Mr. Willson-Pepper's letter last week it would seem that I did not make myself clear regarding the cause of leg ulcers in my series (April 26). In 10·4% it was the cause of failure of the leg-muscle pump and not the cause of ulceration which was doubtful.

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1. McGill, R. J. *Lancet*, 1951, i, 1018.
2. *Lancet*, 1951, ii, 1025.
3. *Medicina, B. Aires*, 1949, 9, 397.
4. Lanari, A., Molins, M., Croxatto, O. *Ibid*, 1951, 11, 12.
5. Musselman, M. M. *War. Med.* 1945, 8, 325.

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1. Fargel, H. *Munch. med. Wschr.* 1951, 93, 602.

Mr. Willson-Pepper refers to a definite group of patients in whom only ulceration, skin changes, and gross varicosities can be found and who are benefited by "a carefully planned operation." If these patients have no deep insufficiency as Mr. Willson-Pepper believes, why have they ulceration and skin changes unlike many patients with gross varicosities who have no ulceration? Verneuil,[1] Gay,[2] Lockhart-Mummery and Smitham,[3] and Moore [4] have demonstrated dilatation of the deep veins in such patients as Mr. Willson-Pepper describes. Moreover there is a thrill on coughing palpable over the varicosities of such patients with ulcers which cannot usually be felt in those with gross varicosities and otherwise healthy legs. This suggests that the valves in the deep veins are incompetent in the former group.

While not doubting that some of the group described by Mr. Willson-Pepper benefit by operation (and perhaps by the rest and bandaging following it), my experience is that most relapse in a few years unless elastic stockings have been worn, and that this relapse is from failure to treat the basic cause—namely, the deep venous incompetence.

Leeds. S. T. ANNING.

POSSIBLE DANGER WITH CYCLOPROPANE

SIR,—I have read with interest the correspondence on this subject. The hexagonal nut on the cyclopropane cylinder should be kept tightened; it will then be almost impossible to turn the key accidentally. Keys other than the circular variety are a menace and should be banished from the theatre.

Royal Hospital, Wolverhampton. J. F. RICKARDS.

REACTION TO PROCAINE PENICILLIN

SIR,—Dr. Yuval's letter of Jan. 19 prompts me to report a rather similar case.

A young man, with an incipient infection of the lower mandible, was sent by me to hospital with instructions to give him 300,000 units of procaine penicillin. A few minutes after the injection his hands and feet began to twitch, and he had difficulty in ringing for the nurse. He did not lose consciousness. The injection was made with the patient in bed, and the nurse said that she withdrew the syringe plunger before the injection and that there was no blood. The resident doctor found the patient severely shocked and gave him leptazol. When I saw him some fifteen minutes later he was in obvious distress. His diaphragm was apparently spastic, and he could hardly breathe. He was fairly cyanotic. When I tried to take his blood-pressure my sphygmomanometer did not register anything. His heart-sounds were hardly audible. I gave him oxygen intranasally. Immediately he told me that his breathing was easier, but the tension in the mid-abdomen continued. He was perfectly all right in about two hours, except that he felt tired. I gave him procaine penicillin a year ago with no untoward results.

After this incident I had the patient patch-tested for procaine and penicillin separately, with negative results.

In view of the fact that thousands of procaine penicillin injections are given and very few reactions have been reported, I wonder if these are due to the drug entering the blood-stream immediately. After all, the only method of ascertaining whether the needle has perforated a vein is not entirely foolproof. I believe that if a thick needle passes right through a vein, the tip of the needle being in muscular tissue, aspiration would not yield any blood. The drug is then injected, and when the needle is withdrawn it may perhaps permit some of the drug, which is under pressure at the site of the injection, to penetrate into the vein.

Shanghai, China. V. P. SMOLNIKOFF.

SELF-DEMAND FEEDING OF INFANTS

SIR,—I have read with interest the article by Professor Illingworth and Dr. Stone on self-demand feeding in a maternity unit (April 5).

I feel sure that self-demand feeding in the maternity unit will cause the mother to feel confident and contented by the time she leaves the hospital, so that many feeding difficulties now encountered in the infant-welfare clinic will not arise. By this time the baby will practically have adopted "its own intrinsic pattern of feeding behaviour," so that the mother will be able to regulate her daily routine at home. Thus she will have no more work than if she feeds by the clock.

If more maternity hospitals would adopt the idea put forward by Professor Illingworth and Dr. Stone and especially the idea of allowing the baby to be kept in a crib beside the mother day and night, I am sure that we should have the mother well on the way to knowing her baby in all its moods, instead of mother and baby leaving hospital nearly strangers.

Pan, Weedon Lane,
Amersham, Bucks. ANN MOWER WHITE.

BRAIDED TANTALUM WIRE

SIR,—I was interested to read of the experience of Mr. Howkins and Mr. Hans with braided tantalum wire (May 10).

Mr. Blacow Yates and I have not used braided tantalum wire, but for some years we have commonly used stainless steel wire for closure of the abdomen (including peritoneum) and repair of herniæ, &c. Our cases have been singularly free from trouble; in only two did the wire require removing—in one owing to a persistent sinus and in the other on account of a pricking sensation felt in the skin over the superficially placed knot. In this second case only the knot had to be removed, and it taught us that knots beneath the skin are unnecessary and must be avoided.

Like all users of stainless steel wire, we find that unless it is carefully handled it kinks and breaks at the kink. This disadvantage has been overcome, however, by using braided stainless steel wire. We have used the finer sizes (42–44) of plain stainless steel wire for intestinal and ureteric suture, and find them eminently satisfactory.

All our stainless steel wires are of the finest quality procurable, and were kindly made for us by Messrs. Samuel Fox Ltd., of Stocksbridge, Sheffield.

Royal Hospital, Sheffield. DAVID AIKEN.

WEIL'S DISEASE TREATED WITH PENICILLIN

SIR,—May I add a few remarks to Dr. Broom's criticism (Feb. 9) of the therapeutic value of penicillin in Weil's disease, which was claimed by Dr. Herbert-Burns and Mr. Flavell.[1] I entirely agree with Broom's views on penicillin, but I think that very grave doubt should be cast on the *leptospiral* origin of the case under discussion:

1. The presence of leptospires in the urine as early as the 5th day of illness is most unusual, and would be very improbable in a human infection with *Leptospira icterohæmorrhagiæ*. The difficulty of recognising leptospires in blood or urine by dark-field microscopy is well known, as is the fact that workers who are inexperienced in leptospiral research may easily mistake artefacts, especially blood-filaments ("pseudo-spirochætes"), for leptospires.

2. The continued absence of leptospiral agglutinins in the patient's serum for $2^1/_2$ months after the onset of disease would practically exclude the possibility of a leptospiral infection if, as was done here, the tests were carried out with different type-strains of leptospires. A few instances have been reported in which the production of antibodies was delayed, but positive titres always developed in these cases by the end of a month.

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1. Verneuil, A. *Gaz. méd. Paris* 1855, 10, 531.
2. Gay, J. On Varicose Diseases of the Lower Extremities. The Lettsomian Lectures of 1867. London, 1868.
3. Lockhart-Mummery, H. E., Smitham, J. H. *Brit. J. Surg.* 1951, 38, 284.
4. Moore, H. D. *Lancet*, 1951, ii, 7.

1. Herbert-Burns, J., Flavell, H. C. G. *Lancet*, 1951, ii, 1142.

The case of Weil's disease described by Garnier and Reilly,[2] to which Dr. Broom refers, was investigated in the early days of leptospiral research, and no agglutination reactions were performed. These authors used a protection test, and concluded that no immune bodies were present on the 29th day of illness. In my view these results should not be taken to imply that the absence of protective antibodies also proves the absence of agglutinating antibodies.

Leptospira Research Laboratory,
Institute for Tropical Hygiene and
Geographical Pathology,
Amsterdam.

J. W. WOLFF.

AN UNUSUAL AORTIC MURMUR

SIR,—A fit young man of 23 was referred to hospital for the assessment of a murmur in the aortic area. He was symptomless and played strenuous games without disability.

Five years previously he had appeared before a National Service Medical Board. He was examined standing up, told he had a heart murmur, and referred to a specialist. The specialist examined him lying down, said he had no murmur, and graded him A1. He served in the R.A.F. without disability for two years.

Recently he had been medically examined before being accepted for employment in a bank. A murmur was again heard and was loudest just below the right clavicle.

No abnormality was found outside the cardiovascular system. In the supine position, both radial pulses were normal and the blood-pressures equal at 110/75 mm. Hg. The heart was not enlarged. A murmur could not be heard in this position nor could one be induced by turning him to the left.

There was a remarkable change in signs with the patient sitting or standing. A harsh systolic murmur became audible, loudest below the middle third of the right clavicle and well conducted to the apex and along the right common carotid and subclavian arteries. The right radial pulse became smaller than the left and the blood-pressure in the right arm fell to 95/80. The murmur ceased abruptly on full expiration when the blood-pressure and pulse in the right arm returned to normal, and again on full inspiration when the radial pulse was obliterated. No such changes occurred in the right common carotid artery.

It was obvious that the murmur was arising in the right subclavian artery and was caused by its partial compression in the neck in the upright position. The murmur disappeared when the artery was obliterated during full inspiration, and again when all compression ceased during full expiration or when the patient was lying down.

No cervical rib was present, and apart from the signs I have described there was no evidence of a thoracic-outlet syndrome. The artery was probably compressed as it crossed either a fibrous band or a normal first rib. In cervical or first-rib syndromes a murmur may be heard over the subclavian artery, but I am unaware that a case may present with a murmur as the only finding.

Chichester.

JOHN D. WHITESIDE.

CONFINEMENT IN HOSPITAL

SIR,—In your annotation (May 3) on this subject, which was discussed at the congress of the Royal Sanitary Institute, Mr. Rufus Thomas is cited as seeking to cure the under-employment of midwives and the under-establishment and overworking of trained hospital staff, by bringing the midwife into the hospital for part of her time.

But what of the areas in which both hospital and district midwives are under-established and overworked? The present maldistribution of midwives should engage the urgent attention of the administrators of the National Health Service. In a national service there can be no justification for there being some areas where any woman who desires it can have her baby in hospital, while there are other areas with insufficient obstetric beds adequately to deal with abnormalities. It is in the latter areas, where the needs are greatest, that most difficulty in the recruitment of both district and hospital midwives is experienced.

Over-all establishments (domiciliary and hospital) should be based on the number of live births in the area, with an extra allowance for areas with a poor housing standard, for it is in such areas that the abnormality-rate is highest. (The incidence of pre-eclampsia and prematurity alone, among the abnormalities, has been estimated in America at as much as 400% greater among the low-income groups, and their care calls for at least 400% more skilled nursing-time than is required for the care of a normal case.) Under present conditions there is a vicious circle, in that the unsatisfactory working conditions in understaffed areas make the more fortunate areas all the more attractive.

Administrative unification of the maternity services should be the first step towards ironing out the present unevenness.

General Hospital,
South Shields.

TERENCE G. ROBINSON.

Parliament

National Health Service Bill in the Lords

SPEAKING at the second reading of this Bill in the House of Lords on May 6, Lord WEBB-JOHNSON said that it was idle to pretend that the social services were not linked with the country's financial position; the financial side must be the nation's deepest concern at the present time. He welcomed the Bill, not only as a contribution to economy, but also because he believed that it would have a salutary effect. Moderate charges would lead to a more reasonable use of the health service. Waste and greed—two dangers always associated with the offer of something for nothing—would be diminished. When the pressure on doctors and dentists was to some extent relieved, and when demand was cut down, an improvement might be expected in the quality of the service. He would go even further than the Government in this matter. He had never been able to understand why inpatients in hospitals should be exempt from charges. Taken by and large the inpatients of hospitals today were better able to pay than any other people who made claims on the National Health Service.

QUESTION TIME

New Drug for Tuberculosis

Mrs. JEAN MANN asked the Secretary of State for Scotland how far experiments were being made in Scotland with the new tuberculosis drug, isonicotinic acid hydrazide; and with what results.—Mr. JAMES STUART replied: In coöperation with the Medical Research Council clinical investigations into the therapeutic value of this drug are being undertaken by the research committee of the Scottish Tuberculosis Society. Trials are planned at six Scottish hospitals prominent in the treatment of tuberculosis, but results cannot be expected for some months. Mrs. MANN: Can the drug be obtained by the ordinary medical practitioner, who may pass it on to his patient irrespective of its possible effects? Mr. STUART: It can be prescribed by doctors; but it will not be used by hospitals under the National Health Service until these trials have been completed. Mrs. MANN: But are not these doctors working under the National Health Service and is it not rather risky that they should be allowed to prescribe the drug, since it has not yet been pronounced upon? Mr. STUART: I agree. I should have thought it would have been wiser to await the result of the trials.

Fluoridation of Water-supplies

Mr. S. P. VIANT asked the Minister of Housing and Local Government whether, in fluoridation of water-supplies, the fluorine was added in the form of salts, or in what other form it was added.—Mr. HAROLD MACMILLAN replied: In this country fluoride is not yet added to water-supplies. In the United States of America, however, there is a growing practice to make such an addition and the fluoride is usually added as sodium fluoride, sodium silico-fluoride (fluosilicate), or hydrofluosilicic acid. The first two of these compounds are solid salts, but are usually made into an aqueous solution before adding to the water. Hydrofluosilicic acid is purchased as an aqueous solution.

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[2] Garnier, M. Reilly, T. *C.R. Soc. Biol. Paris*, 1917 80, 101.

Questions on the M.R.C.

Mr. R. J. MELLISH asked the Prime Minister if he would arrange for questions on health matters addressed to the parliamentary secretary to the Ministry of Works, as representing the Lord President of the Council, to be answered by the Minister of Health.—Mr. WINSTON CHURCHILL replied: The Lord President of the Council is responsible to Parliament for the work of the Medical Research Council and questions about that body should be put down to the parliamentary secretary to the Ministry of Works as representing the Lord President. Questions on health matters generally should not, of course, be addressed to the Lord President of the Council but to the Minister of Health.

Mr. MELLISH: Is it not ridiculous that the Minister of Works should be answering questions on cancer research, for example? Is it not about time that the whole matter was looked at again.

THE PRIME MINISTER: I cannot think that this is an urgent matter, although it has become very topical.

Foot-and-mouth Disease

In answer to questions the Minister of Agriculture, Sir THOMAS DUGDALE, stated that the present situation was serious, but it was certainly not unprecedented, and, unless it deteriorated seriously, he had no doubt that it could be brought under control. Since November, 1951, there had been 258 outbreaks of the disease in this country. This should be compared with the experience of Denmark, where 26,000 outbreaks have occurred in the last six months, and that of Holland, where there have been 23,000 in roughly the same period. Western Germany had suffered much more severely. There the total number of outbreaks in 1951 was 155,000. The outbreaks that occurred in the United Kingdom in the winter of 1937–38 and in 1941 were comparable in severity to the present one, and there were much more serious outbreaks in each of the years 1922–24 and in 1942. In every case the disease was stamped out, to the immense benefit of the flocks and herds in this country, of meat and milk production, and of our valuable export trade in pedigree stock.

Movement and marketing restrictions had been imposed over most of Great Britain because of the danger of infection having been spread through two markets. This was purely a holding operation while the veterinary staff of his department were tracing and keeping under observation the animals concerned, which had been dispersed over a wide area. When that operation had been completed, he hoped that it would be possible to make substantial reductions in the area under control.

He had no evidence that the virus of the present outbreak of foot-and-mouth disease was new. It had been identified as type A. Recent experience on the Continent with this virus had shown that a number of animals, particularly young animals, died, and the time taken by others to recover varied considerably. He asked the House to accept his earnest assurance that there was no question whatever that, in the present state of our scientific knowledge, the abandonment, or even relaxation, of the slaughter policy would involve the livestock industry of this country in the gravest disaster since the days of the cattle plague of the 19th century, with incalculable consequences to our meat and milk supplies. All responsible agricultural organisations were emphatic in the view that the slaughter policy was the best method of dealing with the disease in this country.

Hire-purchase of Doctors' Cars

In answer to a question, Mr. P. THORNEYCROFT stated that to assist doctors in their service to the public, he would consider applications for licences from doctors in or entering general practice who do not own and have not recently owned a car, allowing them to pay off the balance of the purchase price in a longer period than the maximum of 18 months laid down in the Hire-Purchase and Credit Sale Agreement (Control) Order, 1952. Applications would not normally be considered for cars costing more than £800, and the maximum period for repayment would be three years. Doctors who satisfied these conditions might apply for licences through their professional organisations or direct to the Board of Trade.

Unit for Ocular Tuberculosis

Mr. ANTHONY GREENWOOD asked the Minister of Health how many cases of ocular tuberculosis were known to his department: and what steps he is taking to acquaint medical boards with the fact that such cases can now be treated in the ocular tuberculosis unit at Swanley, Kent.—Miss PATRICIA HORNSBY-SMITH replied: This condition is not separately notifiable and the number of cases is not known; the present waiting-list for the unit is 7. The availability of the unit is generally known through the hospital service, and at the present experimental stage special publicity seems neither necessary nor desirable. Since it opened on June 7, 1951, patients have been admitted. Twenty beds are at present occupied.

Broadmoor Institution

Lieut.-Colonel MARCUS LIPTON asked the Prime Minister whether he would consider the transfer of responsibility for the internal control of the Broadmoor institution from the the Ministry of Health to the Home Department.

Mr. WINSTON CHURCHILL replied: Responsibility for the management of Broadmoor was transferred from the Home Office to the Board of Control by Section 62 of the Criminal Justice Act, 1948. As at present advised, H.M. Government are not aware of any reason which would justify them in proposing a reversal of the decision so recently taken by Parliament.

Mr. IAIN MACLEOD, the Minister of Health, announced that arrangements had been made for further investigation of the problems raised by the recent incident at Broadmoor. Mr. J. Scott Henderson, Q.C. (chairman), Captain C. Waterhouse, M.P., Mr. K. Younger, M.P., and Dr. P. K. McCowan were "to inquire into the adequacy of the security arrangements at Broadmoor and to make recommendations."

Public Health

Ways of Learning Public Health

How drowsily we sat, as students, through talk of drains and dustbins, the long hopper, the short hopper, the inspection of meat, and the water-supply; and that was public health. Today, at the London School of Hygiene and Tropical Medicine, they do it rather differently. True they are dealing with full-blown graduates, and not mere larvæ; but even the postgraduate course has changed in tempo, content, and variety. Prof. J. M. Mackintosh, in the report on the work of the school for 1950–51, remarks that he and the staff of his department are becoming more experienced in providing for the needs of a heterogeneous group [illegible] students; and certainly they offer something suited [illegible] every taste.

[illegible] three-month introductory course to the subject [illegible]ened by early visits to see the work of [illegible] WEIL'S DISEA[illegible]rities at Luton and Watford. This SIR,—May I [illegible]adlarly helpful to students from overseas, [illegible]icism (Feb. 9) touch with the rapid developments in Weil's dis[illegible] central government. Study groups are [illegible]s an[illegible] during the first term, to follow up various [illegible]ts. Students are not expected to undertake proper field investigation, for that is an elaborate task; the aim is rather to get them to work well together as a team, and to learn something of methods of research under the eye of a sympathetic teacher. During the year reviewed there were eight subjects for study.

Since it was the Festival year, the school decided to prepare its own exhibition, and one group took an active part in choosing and arranging sections on child health, the social services, and the pioneers of public health, through the century. Each student took one special part of the study, and worked out the details; which meant reading official publications, white-papers, biographies, and textbooks, and visiting Government departments to check facts. Finally the group opened the exhibition to the rest of the class, and stood by to answer questions.

Meanwhile a group on juvenile delinquency, composed of 5 students and 2 health visitors, inquired into the functions of the remand home. They visited six such homes, analysed and discussed their collected data, and came to the conclusion that the homes ought to be classified. They condemned the practice of housing together in remand homes young people ing periods of punishment, mental defectives, prostitutes he making, and children needing care and protection se results, too, were presented to the rest of the class. tudy group on housing were invited to contribute to a er survey, being carried out by the Ministry of Health, the social problems and needs of families living in large cks of flats. They made a detailed study of 34 flats in post-war municipal housing estate in Hornsey, and found m good, the rents reasonable, and the tenants satisfactory. ey made some suggestions, based on the opinions of the ants, about details of internal design, and playing facilities young children; and presented their report to their leagues in the manner of a broadcast programme, represent- the voices of the tenants giving their views on the flats. more serious report was sent to the Ministry of Local vernment and Planning.

A group of 9 students and 2 industrial psychologists studied ablement schemes under three Government departments d in selected voluntary organisations. After visiting spitals and training and reablement centres they decided at the provisions for helping disabled people back to work e comprehensive, but that in some cases the machinery either too flimsy or too ponderous to deal with a delicate oblem. A study group on history investigated the develop- ent, during the 19th century, of sanitary administration in ottenham, which—as a rural parish—had a well-organised nitary service before it became an urban and industrial ntre, though it went through a period of chaos during its pid urban growth. A report of this study was published y the medical officer of health for Tottenham in his annual port for 1950.

A group set to consider the training of the sanitary inspector relation to his duties concluded that there should be a ingle statutory qualification, and a register, and that the xamination should be conducted by the universities. An ttempt was made, with another group, to reproduce in niniature the conditions of a field survey; and a study was nade of school absence among a group of children in Wembley. ver 20% of the absences were found to have no medical ause. Where the mother was employed there was less absence from medical causes among the children than among hildren whose mothers did not go out to work. Professor Mackintosh notes that it would be interesting to discover more about this finding. Finally, a study group on tuberculosis followed up 50 recently notified cases of tuberculosis to discover something of the quality and quantity of the service received. They concluded that there was a serious lack of coördination between the authorities and the people providing preventive and curative services in the area. They also mentioned lack of equipment in the clinic, and apparent lack of diligence in tracing contacts.

In their second and third terms the students, besides doing their group work, took up elective studies in industrial health, hospital administration, or local government. Seminars, for group discussion, were also arranged. The department now plans to work in association with a field area, and is negotiating for this purpose with the south-west division of Hertfordshire.

Suspected Smallpox in a Ship

Chickenpox has been finally diagnosed in a patient who came ashore at Swansea on April 23 with suspected smallpox.

Variola Minor in South-east Lancashire

The last case of variola minor in the outbreak in the Rochdale area occurred at Middleton: the patient was removed to hospital on April 17. All districts have now been declared free from smallpox infection. At the beginning of this week two convalescent patients remained in hospital and were awaiting discharge. A formal announcement that the country was free from infection was expected on May 15.

Estimate of Future Births

The Registrar-General's[1] final estimate of live births to be expected in the quarter ending June 30 is 175,000, and his provisional estimate of the number in the quarter ending Sept. 30 is 172,000. The totals in the corresponding quarters last year were 180,958 and 168,028.

Obituary

HARRY CAINE BOYDE

M.B. Lond.

Dr. Boyde, who died on March 29 at the age of 48, had spent most of his working life, since he qualified from Barts in 1925, as a general practitioner near the London Custom House. Outside his practice, he had a special interest in industrial medicine, and he was medical officer to the River Thames Ship Repairers' Association. His quarterly sickness reports were probably the only index of dock health in the country.

S. T. writes: "Harry Boyde was no ordinary general practitioner. He worked in dockland from choice, for he felt at home with the dockers and they elected him vice-chairman of their trades council; and here he could smell the sea, which, after socialism, was his second great love. Working-class industrial practice is not easy. Boyde gave his patients a service of the highest order. In the summer he made regular rounds of all the old folk on his list, to check their general health and keep a friendly eye on them, against the busy months of winter when their long-standing needs might tend to get overlooked.

"Not far from his surgery is a new council estate built on an area ruthlessly cleared by the blitz. At Boyde's suggestion, each street is named after a Civil Defence worker killed in the bombing; all of them were old patients. With his colleagues, Boyde built up an excellent rota system, to meet the needs of the people of West Ham, and at the same time give the doctors some much-needed rest. After the war, he worked hard to establish a health centre in a suitable building, a former public-assistance office; but unhappily his efforts failed. To go round with Boyde among his docker patients was a happy experience. They treated him as a friend and an equal, than which they could give no higher honour."

Births, Marriages, and Deaths

BIRTHS

BEATTIE.—On May 1, at St. Bartholomew's Hospital, London, to Bud (née Robarts), wife of Dr. A. O. C. Beattie—a son.

BORRIE.—On May 6, to Helen (née Chesney), wife of Dr. Peter Borrie—a son.

CHALMERS.—On May 2, at Bangour Hospital, West Lothian, to Cynthia (née Field), wife of Mr. T. S. Chalmers, F.R.C.S.E. —a son.

FITZPATRICK.—On May 3, at Guy's Hospital, London, to Eva (née Travers), wife of Surgeon-Commander J. M. Fitzpatrick, R.N. —a daughter.

FRAZER.—On May 5, at Bramhall, Cheshire, to Marjorie (née Lee), wife of Dr. Alan C. Frazer—a son.

HADFIELD.—On May 4, at King's College Hospital, London, to Eileen (née Dexter), wife of Dr. Gordon Hadfield—a daughter.

HEAF.—On April 30, at University College Hospital, to Rosemary (née Cartledge), wife of Dr. P. J. D. Heaf—a daughter.

KENCHINGTON.—On May 7, at Bromsgrove, to Barbara (née Swaffield), wife of Dr. Noel S. Kenchington—a son.

PAYNE.—On May 5, in Edinburgh, to Alice (née McCorry), wife of Dr. J. P. Payne, of Currie—a son.

RUDDELL.—On April 30, at Northallerton, the wife of Dr. John Shegog Ruddell—a son.

STARKS.—On May 1, at Wolverhampton, to Isobel, wife of Dr. J. Michael Starks, of Wombourn—a son.

TALBOT.—On May 5, at Cambridge, to Margaret (née Hooper), wife of Dr. C. H. Talbot—a son.

MARRIAGES

WRIGHT—SMITH.—On May 3, at Addiscombe, Surrey, Basil Martin Wright, M.B., to Sheila Langton Smith.

DEATHS

CARVER.—On May 3, at Wimbledon Close, Norman Clifton Carver, M.B. Camb., late of Surbiton and Ewell, aged 76.

FENNELL.—On May 6, in London, Eric Stanhope Fennell, M.B. Bombay, M.R.C.P.E.

JORDAN.—On May 2, at 17, Wilbury-road, Hove, Bertram Furneaux Jordan, M.B. R.U.I., late of Granton, King's Norton, Worcs, aged 88.

NANDA.—On May 9, at St. Briavels, Glos, Ram Nath Nanda, L.R.C.P.E.

SCOTT.—On May 4, at 29, Curzon Park North, Chester, William Sibbald Scott, M.B. Edin., aged 74.

SHAW-CRISP.—On May 4, Cuthbert Shaw-Crisp, M.R.C.S., of 24, St. Catherines, Lincoln, late R.A.M.C.

SUMNER.—On May 1, at Fir Trees, Buckland Newton, Dorset, F. W. Sumner, M.D. Camb., F.R.C.S.E., lieut.-colonel, I.M.S. retd.

WHARTON.—On May 5, at "Quinta," Hale Barnes, Cheshire, John Wharton, M.A., M.D. Camb.

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[1] Registrar-General's Return for the Week ended May 3, 1952. H.M. Stationery Office. Pp. 20. 1s.

Notes and News

DISTRIBUTION OF TERRAMYCIN

Last week we announced arrangements for the distribution and use of terramycin. Now, additionally, practitioners in the National Health Service may obtain this antibiotic for the treatment of penicillin-resistant staphylococcal infections. Application should be made to the nearest distribution centre (see *Lancet*, May 10, 1952, p. 980).

ROYAL DENTAL HOSPITAL

The 35th annual clinical At Home of the Royal Dental Hospital was held on May 10. The department of photography has been rebuilt during the past year, as also have the departments of dental radiology and pathology. As usual, there was a well-chosen selection of clinical cases. During the morning session Mr. Van Thal gave a demonstration of speech therapy in cleft palate, and also of simple mouth exercises in malocclusion. The hospital has a new inpatient unit at the Grove Hospital, Tooting, where Dr. Bowdler Henry showed his operation for the prophylactic enucleation of uncalcified third molars. In the electrotherapeutic department, Dr. R. H. Leaver showed the results of treatment of acute ulcerative gingivitis by irradiation with a titanium-arc lamp. The initial exposure is for one minute, and the exposure is increased by a further minute at each subsequent visit; healing is rapid and relapses are unknown. The same treatment is also successful in leucoplakia of the tongue. Self-polymerising acrylic resins for restorations in anterior teeth were demonstrated. A new type of dental handpiece, developed in Germany, was also on view; this instrument is claimed to be almost free from vibration—an innovation that will be appreciated by the patient as much as the operator.

In the afternoon there was another meeting of the "Brains Trust," which established itself as a success at the last At Home. The team, consisting of Mr. N. J. Ainsworth, Mr. B. W. Fickling, Mr. J. H. Hovell, and Mr. A. L. Packham, was under the charge of Dr. O. L. Carden Sibley. The questions were, perhaps, more serious than at the previous session, but the team showed a ready wit in dealing with such diverse matters as the advisability of abolishing all tooth pastes and powders, and the right things to say to a patient when the wrong tooth has been inadvertently extracted.

CONTROL OF DRUG-ADDICTION

The third report [1] of the W.H.O. Committee on Drugs of Addiction states that the inquiry into the use of diacetylmorphine (heroin) has shown that 50 member States have stopped, or are willing to stop, its medical use. The committee hopes that it will be possible to abolish completely the legal manufacture of the drug throughout the world; such a step would make it much easier to control its illicit production. The use of cannabis preparations is also considered to be without medical justification. The report recommends that certain synthetic derivatives of pethidine and amidone should be classified as addiction-producing drugs.

LEISURE IN MATURITY

A retired life is usually the last thing wanted by the retired. The long-pursued fantasy of leisure, captured and caged at last, proves poorer company than their former working companions. The *Sundial*, a bi-monthly news-letter, is trying to make a link between retired people and those in sight of retirement—especially Civil Servants, bank officials, teachers, local-government officers, professional men, and commercial and industrial executives. It will give news of interest to readers, establish correspondence circles, open the way to the sharing of pursuits and to agreeable companionship, give some opportunities for the use of the knowledge, experience, and ability of its readers, and (it is hoped) relieve their boredom. Doctors may consider recommending it to patients who are looking forward with misgiving to their retirement. It is published by Mr. J. R. Salter and Mr. A. G. Butcher, M.C., at The Sundial Press, Tithe Barn, Red Lane, Claygate, Esher, Surrey.

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[1] *World Hlth Org. techn. Rep. Ser.* no. 57, 1952. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1. Pp. 14. 9*d*.

AMERICAN ANTIBIOTICS PROGRESS

In the U.S.A. in 1950 one dollar in every four spent on scribed drugs went on antibiotics. 853,000 lb. of medicinal biotics were produced, at a sales value totalling $214 mil. One of the important reasons for the continuing growth antibiotics manufacture is the new market for these substa. as a supplement to animal feed. The big four in feed aureomycin, terramycin, bacitracin, and penicillin; and Messrs. Lederle (American Cyanamid) estimate that as much aureomycin is going into feed as for medicinal purposes. Despite all research there is no news of the effective and avail antibiotics being increased beyond the present six or eight penicillin, streptomycin, bacitracin, chloramphenicol, aureomycin, and terramycin (to which neomycin and viomy may be added). In the production of penicillin, new pl that are being set up by five manufacturers are expected t double 1951 capacity, which itself was triple that of 1949

A NEW VENTURE FOR THE DISABLED

The leisure to make something is one of the few compensations a serious disability brings with it. Many of the disabled would like to sell the things they make, not only because most of them need the money but because it is good for the spirit to contribute, even on a small scale, to the country's common store. Their trouble, usually, is to find a permanent market, for when their friends have bought as many baskets, stools, gloves, or handbags as they can reasonably afford the disabled worker has no way of finding a wider clientele. A growing enterprise, launched at Oxford, has been planned to overcome this difficulty. The Oxfordshire Association of the Helping Hand for Handicapped Workers [2] was formed by a voluntary committee in 1950, to help those who are too severely disabled to be registered under the Disabled Persons (Employment) Act, 1944, as well as those who are registered but live where no sheltered conditions of employment are provided. They were able to open a stall in Oxford Market kindly let to them at a low rent by the City Council. The stall was reconditioned by the patients and staff of Headington Hill Hall Rehabilitation Centre, and a generous trader installed electric lighting. Then various voluntary societies, occupational therapy departments, and local authorities were notified, and notices were put in appropriate journals announcing that patients fulfilling the necessary requirements, and with medical approval, could send their goods on sale or return to the stall at Oxford. Goods are accepted from anywhere in the British Isles. An immediate response, especially through the British Red Cross Society, produced enough goods of high standard for the stall to be opened in September, 1950, and it has proved so successful that 60% of the original workers still send goods regularly, and a further 10
Over 2250 articles were sold in the first thr
about 30 had to be sent back unsold. The
goods rose from about 100 at the start to 285 last September.

This kind of undertaking needs businesslike management. The departmental buyers in one of Oxford's main stores offered themselves, with the consent of the proprietor, as members of a selection and pricing committee; and a system of accounting was planned by a member of a firm of chartered accountants, himself disabled, who acts as treasurer. The stall and reception store are staffed by voluntary workers, the stall being open from 10 A.M. to 4 P.M. on three days a week.

The association are hoping to develop the scheme until they have formed a national body, with a central council and branches all over the country. Wherever plans are being made to open a shop for the sale of disabled people's work the name "Helping Hand" may be used if the shop is run on the main lines of the Oxfordshire plan: that is, goods should be accepted on a sale-or-return basis, and only from people whom a recognised authority vouches to be too disabled to be insurably employed; and a committee of professional buyers should be appointed to reject inferior work and price the work accepted. Those proposing to open a "Helping Hand" should get in touch with the association first, in case another shop is opening in their area. The first branch shop was opened at High Wycombe on March 1, and everyone will wish to see this useful and sensible scheme get a footing in other towns. Those interested should write to the Secretary, Oxfordshire Association of the Helping Hand for Handicapped Workers, c/o Headington Hill Hall, Oxford.

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[1] *Chemical Engng, New York*, February, 1952, p. 149.

[2] Report of the Inaugurating Committee, September, 1950–September, 1951.

versity of Oxford

n May 1 the degree of D.M. was conferred on I. V. Polunin.

versity of London

t a recent examination for the postgraduate diploma in hological medicine the following were successful:

M. Cuthill, B. V. Earle, F. J. Fish, Hildegard C. Fisher, M. H. dman, J. L. Gibbons, R. C. Gledhill, Julius Guild, Mary L. e, Anthony Hordern, A. G. Hucker, J. G. Jesson, Moyra S. M. np, Anne K. Kirkland, N. P. Lancaster, Felix Letemendia, . Lindsay, Janet N. McCulloch, D. G. McLachlan, John Marshall, W. Moynagh, Dorothea M. Norman-Jones, Wolfgang Pappen- n, R. H. Park, Jafar Mohamed Karim Rehmany, W. J. B. gers, D. J. Salfield, W. K. Schnarr, J. R. Smythies, J. B. Stanton, auel Stein, K. F. Weeks, D. J. West (with special knowledge of ntal diseases); J. B. Jeffries, M. P. Nelson, E. W. Shepherd th special knowledge of mental deficiency).

iversity of Birmingham

Prof. Boris Ephrussi, of the University of Paris, will liver the William Withering lectures on Tuesday, Wednes- y, and Thursday, May 27, 28, and 29, at 4 P.M., at the dical School. He is to speak on Nucleus and Cytoplasm the Genetics of Micro-organisms.

oyal College of Surgeons of England

At a meeting of the council on May 8, with Sir Cecil Wakeley, e president, in the chair, Mr. I. B. Jose (Adelaide) was lmitted to the court of examiners. Mr. E. H. Shaw, Dr. S. A. enry, Mr. V. B. Green-Armytage, Sir William Kelsey Fry, d Prof. John Kirk were admitted to the fellowship, having en elected as practitioners of 20 years' standing. Mr. T. W. Cashell was admitted to the fellowship *ad eundem*.

The Jacksonian prize was presented to Mr. Rodney Smith St. George's) and an honorarium and certificate of honourable ention to Mr. G. O. Jelly (Manchester); the John Hunter edal and triennial prize to Dr. Cuthbert Dukes; and the Begley prize to Miss J. R. Carlton Jones. The first Lister ward in ophthalmology and travelling scholarship was given o Dr. M. E. Langham.

Sir Ernest Finch was appointed Thomas Vicary lecturer or 1953.

Diplomas of membership and diplomas in anæsthetics and n tropical medicine and hygiene were granted to the candidates named in the report of the comitia of the Royal College of Physicians (*Lancet*, May 3, 1952, p. 933). A diploma in child health was also granted to L. I. Phillips.

Royal College of Physicians of Edinburgh

At a meeting of the college held on May 6, with Dr. W. A. Alexander, the president, in the chair, the following were elected to the fellowship:

R. F. Robertson, J. T. R. Russell.

The following were elected to the membership:

Gostha Bihari Sinha, Sunder Balse, Sanatkumar Hiralal Shah, G. F. Hall, M. J. Bailey, Sutcliffe Ruttle, Deb Prasanna Basu, Bal Sitaram Kulkarni, N. M. Mann, D. T. Kay, O. G. Jones, Walter Bolliger, Andrew Macfarlane, N. K. Pein, W. I. Forsythe, W. D. H Conacher, Anilkant Dulerai Desai, Zahur Hussain Nurullah Kadri, Shanti Narain Mathur, R. A. Kershaw, Bermeshwer Prasad, G. S. Kilpatrick, R. J. Connolly, K. L. Stuart, J. A. McLeod, Balbir Singh Khaira.

Royal College of Nursing

Dr. Noel Harris will be one of the speakers at the meeting which the south-east metropolitan branch is holding at the college, Cavendish Square, London, W.1, on Wednesday, May 21, at 7.30 P.M., to discuss the Spiritual Factor in Medicine.

Course on International Medical Law

The first course on this subject is being held by the Bordeaux faculty of medicine. It is being given by Professor Auby.

St. Cyres Lecture

Dr. William Evans will deliver this lecture at 1, Wimpole Street, London, W.1, at 5 P.M. on Wednesday, June 11. He will speak on Œsophageal Contraction and Cardiac Pain.

Retirement of Dr. H. H. MacWilliam

Dr. H. H. MacWilliam will retire from the post of medical superintendent of the Walton Hospital, Liverpool, on June 30, after thirty-nine years' service. A Testimonial Fund has been arranged under the ægis of the hospital management committee, and friends and colleagues who wish to contribute should send their donations to Mr. Colin A. W. Roberts, O.B.E., chairman of the hospital management committee, or Dr. H. Alstead, deputy medical superintendent, at the Walton Hospital, Liverpool, 9.

West Midland Physicians Association

A meeting of this association will be held at the Royal Hospital, Wolverhampton, on Saturday, May 24, at 11 A.M.

Society of Medical Officers of Health

Dr. Andrew Topping has been elected president of this society for 1952–53. He will be installed by the outgoing president, Dr. W. G. Clark, on Sept. 18.

Society for Endocrinology

A one-day symposium on the posterior pituitary will be held on Friday, June 20, at Cambridge. Those who are not members of the society, but who wish to attend, should write to Prof. N. F. Maclagan, Westminster Medical School, Horseferry Road, London, S.W.1.

I.M.S. Dinner

The annual dinner of the Indian Medical Service dinner club will be held at the Connaught Rooms, Great Queen Street, London, W.C.2, on Friday, June 20, at 7.30 P.M. Tickets may be had from the secretary of the club, medical board room, Commonwealth Relations Office, Matthew Parker Street, S.W.1.

Review of Benefit Payable to Inpatients

The Minister of National Insurance has asked the National Insurance Advisory Committee to review the amounts by which the National Insurance benefits of long-term hospital inpatients are reduced.

At present benefit is reduced after eight weeks in hospital by 5*s*. a week if the patient has a dependant and by 10*s*. a week in other cases. After a year in hospital benefit is further adjusted, leaving the patient with 10*s*. a week if the treatment is for respiratory tuberculosis and with 5*s*. a week in other cases. If the patient has a dependant the balance may be paid to the dependant.

Organisations or persons who wish to submit material to the committee should write to the secretary, 30, Euston Square, London, N.W.1, before Friday, June 20.

International Congress of Physical Medicine

The scientific programme of this congress, which is being held at King's College, Strand, London, W.C.2, from July 14 to 18, will be opened by a Review of Physical Medicine in the Past Decade in which F. D. Howitt, F. H. Krusen (United States), S. Clemmesen (Denmark), and V. E. Klare (Austria) will take part. Other subjects and speakers will include: Physical Education (E. Grandjean, Switzerland, J. H. Kuitert, United States); Rehabilitation and Resettlement (Howard A. Rusk, United States, P. Houssa, Belgium, F. S. Cooksey); Management of the Chronic Rheumatic and other Disorders of the Locomotor System (Sir Henry Cohen, L. J. Michotte, Belgium, H. A. W. D. Fletcher, D. A. Kininmonth, S. Mattingly); Electrodiagnostic Methods (J. Lefebvre, France, E. Kugelberg, Sweden, P. Bauwens). Further particulars may be had from the honorary secretary of the congress, 45, Lincoln's Inn Fields, London, W.C.2.

Fifth World Health Assembly

Dr. Brock Chisholm, director-general of the World Health Organisation, in his annual report to the Assembly, which opened in Geneva on May 8, said that 1951 had seen the gradual and unmistakable stirrings of a "world health conscience." It was not enough for a few nations to produce, for example, antibiotics or insecticides simply for their own use, leaving others to their own inadequate resources. The manufacturing countries must either produce a surplus for export, or help other people to make their own supplies. Investment in international health through W.H.O. was beginning to yield dividends, not yet great but nevertheless tangible. Many examples could be given: more than a million people in Indonesia had been examined for signs of yaws in the past 18 months, and over 150,000 had been treated; another half-million had been examined in Thailand; and as many again in Haiti "where, 8 months after the mass campaign was completed, no case of infectious yaws was found."

At another session Sir Herbert Broadley, deputy director-general of the United Nations Food and Agriculture Organisation, pointed out that the very success of W.H.O.'s efforts to reduce mortality had underlined F.A.O.'s task of increasing food-supplies to keep pace with a mounting world population. As the populations of the food-growing countries expanded, the fall in the surplus of food for export might mean serious shortages in the highly industrialised areas of the world.

Royal Sanitary Institute Health Congress

Next year this congress will be held in Hastings from April 28 to May 1.

Industrial Accidents

On Wednesday, May 21, at 2.30 P.M., Mr. H. R. Payne, chairman of the national industrial safety committee of the Royal Society for the Prevention of Accidents, will speak on this subject at the Royal Society of Arts, John Adam Street, London, W.C.2.

National Marriage Guidance Council

The council will hold its annual conference at Bournemouth from May 22 to 25. The speakers will include Mrs. Clara Stewart, M.B., Dr. Doris Odlum, and Dr. Eustace Chesser. Further particulars may be had from the secretary of the council, 78, Duke Street, London, W.1.

Convention of Nobel Laureates

The second convention of Nobel prize winners will be held from June 23 to 27 in Lindau-Bodensee, Switzerland. The programme includes the following lectures: Professor v. Hevesy (Stockholm), Application of Radioactive Indicators for Research into the Processes inside the Animal Body; Prof. A. Butenandt (Tubingen), Experiments with Insect Hormones; Prof. G. Domagk (Wuppertal), Chemotherapy in Tuberculosis; Prof. R. Kuhn (Heidelberg), Milk Vitamins. Further particulars may be had from Dr. F. V. Hein, Lindau-Bodensee, Fischergasse 37.

Summer School at Strasbourg

The British Social Biology Council are holding at the University of Strasbourg from Aug. 6 to 20 a school on the Healthy Family. Dr. Alfred Torrie will speak on Human Relationships within the Family, and Dr. J. L. Burn on the Health of the Family and the Community. Inquiries should be sent to the secretary of the council, Tavistock House South, Tavistock Square, London, W.C.1.

Congress on Fertility and Sterility

In 1951, in Rio de Janeiro, Brazil, delegates from twelve *nations founded a new society known as the International* Fertility Association. The first world congress sponsored by the new society, in conjunction with the American Society for the Study of Sterility, will be held in New York in May, 1953. Further information may be had from Dr. Carlos D. Guerrero, secretary-general, Miguel E. Schulz no. 19, Mexico, D. F., or from Dr. Abner I. Weisman, associate secretary-general, 1160, Fifth Avenue, New York, N.Y.

EMERGENCY BED SERVICE.—In the week ended last Monday applications for general acute cases numbered 930. The *proportion admitted* was 90·4%.

Lieut.-Colonel D. N. Nicholson, F.R.C.P.E., has been appointed surgeon to the Queen's Body Guard for Scotland, Royal Company of Archers, in succession to the late Lieut.-Colonel J. R. C. Greenlees.

Appointments

ANDERSON, D. A. R., M.B. St. And.: M.O., Barlinnie Prison, Glasgow.
BRENNEN, R., M.B. Belf., D.P.H.: deputy M.O.H. and asst. county M.O., Rochester and Chatham.
HUGHES, G. O., M.C., M.B. Lpool, D.P.H., D.I.H.: chief M.O., North Western Gas Board.
MACMICHAEL, NEIL, M.D. Edin., F.R.C.P.E.: part-time physician, Queensbury House, Edinburgh.

Appointed Factory Doctors:

ANDERSON, CATHERINE, M.B. Edin.: Lochwinnoch district, Renfrew.
BOYLE, D. S., M.R.C.S.: [illegible] Southampton.
HOOSON, T. G., M.B. Lon[illegible] ife.
MCCRAE, J. S., M.B.E., M.[illegible] ict, Ayr.
MACDONALD, D. R., M.B. [illegible] Nairn.

Western Regional Hospital Board, Scotland:

DEVINE, D. C., M.D. Glasg.: S.H.M.O. for regional duties in dermatology.
SCOBIE, J. D., L.R.C.P.E., D.A.: asst. regional anæsthetist.
THOMSON, G. R., M.B. Glasg., F.R.C.S.E., F.R.F.P.S.: surgeon and medical superintendent, West Highland Hospital, Oban.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Diary of the Week

MAY 18 TO 24

Monday, 19th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W
4 P.M. Dr. George Fearnley: Gout.
GUY'S HOSPITAL, London Bridge, S.E.1
5 P.M. Dr. Alfred Blalock: Cardiovascular Surgery. (C lecture.)
ROYAL EYE HOSPITAL, St. George's Circus, S.E.1
5 P.M. Dr. T. H. Whittington: Convergence, Converg Abnormalities, and Heterophoria.

Tuesday, 20th

ROYAL EYE HOSPITAL
5 P.M. Prof. Arnold Sorsby: Surgery of Glaucoma.
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8.30 P.M. *Section of Surgery.* Dr. Blalock (Baltimore), W. R. Bott, Dr. S. J. Crowe (Baltimore), Mr. R. Handley: Halsted Centenary.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W
5.30 P.M. Brigadier J. S. K. Boyd, F.R.S.: Bacteriol Typing and Epidemiological Problems. (Jenner lectu
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hosp Medical School, W.2
5 P.M. Mr. D. W. Henderson, D.SC.: Pathogenesis of Exp mental Pulmonary Anthrax.
INSTITUTE OF DERMATOLOGY, St. John's Hospital, W.C.2
5.30 P.M. Dr. F. T. G. Prunty: Some Effects of Adrenal Cort Hormones in Man.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Dr. A. Anderson: Problems Connected with Old Age.

Wednesday, 21st

POSTGRADUATE MEDICAL SCHOOL OF LONDON
11.15 A.M. Medical clinical-pathology conference.
INSTITUTE OF CHILD HEALTH, The Hospital for Sick Child Great Ormond Street, W.C.1
5 P.M. Dr. Blalock: Treatment of Congenital Heart-disease.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn R W.C.1
5 P.M. Dr. Crowe: Use of A.C.T.H. and Cortisone in Clin Otolaryngology.
ROYAL SOCIETY OF MEDICINE
8.15 P.M. *Section of General Practice.* Dr. J. H. Gibbe Child Management.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Medical Mycology—Pathog Fungi.
ROYAL [illegible] OF EDINBURGH, 18, Nicolson St
3.30 [illegible] almsley: Development and Gro Disc. (Struthers lecture.)
UNIVERSITY OF GLASGOW
8 P.M. (Department of Ophthalmology.) Dr. Paul Baes Experimental Retinal Grafting.

Thursday, 22nd

UNIVERSITY OF LONDON
[illegible] Hygiene, Keppel Street, W.C [illegible] York): Transformation React of three lectures.)
[illegible] OF LONDON
[illegible] ple Lesions at the Cardia.
ROYAL EYE HOSPITAL
5.30 P.M. Miss M. Savory: Cortisone in Ophthalmology.
ROYAL SOCIETY OF MEDICINE
5 P.M. *Section of Urology.* Mr. D. S. Poole-Wilson, Mr. D. In Williams: Chronically Dilated Ureter.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL
5 P.M. Dr. Desmond Curran: Psychiatry lecture-demonstrati
WEST END [illegible] DISEASES
5.30 P.M. [illegible] 48, Cosway Street, N.W Dr. [illegible] of Psychiatry to Gen Medicine.
WEST LONDON MEDICO-CHIRURGICAL SOCIETY
8.30 P.M. (1, Wimpole Street, W.1.) Sir Geoffrey Jefferson, F.R The Brain as an Integrated Machine. (Cavendish lectu
UNIVERSITY OF BIRMINGHAM
4 P.M. (Medical School.) Dr. Helen Payling Wright: Thromb and Embolism.
HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinbur Dr. S. Rowlands: Isotopes as an Aid to Diagnosis.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Prof. W. J. Jessop: Recent Work on Cortisone and Hydrocortiso

Friday, 23rd

POSTGRADUATE MEDICAL SCHOOL OF LONDON
11.15 A.M. Surgical clinical-pathology conference. Mr. J. Kinmonth: Surgery of the Lymphatics. Mr. Allis Malignant Lesions at the Cardia.
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
2 P.M. (*Chelsea Hospital for Women, Dovehouse Street, S.W.* Prof. G. I. Strachan: Early Diagnosis of Gynæcolog Cancer.
4.30 P.M. Mr. Stanley Way: Pathological Anatomy of Lymphatic Spread of Cervical Carcinoma.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. F. R. Bettley: Alopecia.
BIOCHEMICAL SOCIETY
2 P.M. (Physiology Institute, Newport Road, Cardiff.) Scient papers.

Saturday, 24th

INSTITUTE OF [illegible] GYNÆCOLOGY
12 NOON. (Q[illegible] W.6.) [illegible] for Tubo-ovarian Physiology at [illegible]

THE ELECTRO-ENCEPHALOGRAM IN DOUBTFUL CASES OF EPILEPSY*

ERIC C. O. JEWESBURY
D.M. Oxfd, M.R.C.P., D.P.M.
ROLOGIST, ROYAL NORTHERN HOSPITAL, NORTH MIDDLESEX PITAL, AND CHASE FARM HOSPITAL; LATE SENIOR REGISTRAR E.E.G. DEPARTMENTS OF ST. THOMAS'S HOSPITAL AND THE NATIONAL HOSPITAL, QUEEN SQUARE, LONDON

ELECTRO-ENCEPHALOGRAPHY has done much to increase understanding of the epilepsies; but, in spite of rds of caution from workers in this field, there is still airly widespread tendency to overestimate the diagstic value of the electro-encephalogram (E.E.G.) in a ubtful case of epilepsy. A careful clinical record is ll the best evidence of epilepsy; and, when the ignosis is uncertain on clinical grounds, it is exceptional the E.E.G. to produce unequivocal evidence about e nature of the attack. Often in such cases the E.G. merely confuses the issue.

SPECIFIC DYSRHYTHMIAS

The most striking changes in the E.E.G. tend to occur hen the clinical diagnosis is not in doubt. Specific ileptic features in the E.E.G. are seen most often when e patient has petit mal or more than one kind of fit. clinically ill-defined cases the E.E.G. is more likely be normal or to show some non-specific dysrhythmia, may happen in non-epileptic persons. It cannot be o often repeated that many apparently normal people ave an "abnormal" E.E.G. (i.e., show some non-specific rm of dysrhythmia), whereas many epileptics have completely "normal" E.E.G. (i.e., show no sort of regularity). Gibbs et al. (1943) demonstrated several ears ago that almost all electro-encephalographic atterns which might be used for diagnosis could be ound in the E.E.G. of symptom-free persons, and that n about 42% of patients with clinically diagnosed pilepsy a routine E.E.G. was of little or no diagnostic alue.

Occasionally, when the clinician has to depend on an inconclusive description of the patient's attacks, the E.E.G. may help to establish or disprove a diagnosis of petit mal. For instance:

A girl, aged 14, was brought to hospital because in the previous two months she had often dropped things. Her mother had noticed no change in her appearance at the time, there had been no other incidents suggesting blank spells, and there was no relevant family history. A tentative diagnosis of petit mal was confirmed by the E.E.G., which showed classical wave and spike outbursts both at rest and during overbreathing.

The E.E.G. is always abnormal during clinical epileptic seizures and this may be helpful in distinguishing hysterical manifestations from petit mal.

The non-epileptic nature of a patient's attacks was thus confirmed by the fact that his record remained completely stable during the course of several so-called "blackouts," which he said he experienced while the E.E.G. was being made.

It is, of course, exceptional for patients to have a grand-mal attack during ordinary electro-encephalography, but clinical petit-mal attacks, associated with wave and spike complexes in the E.E.G., are fairly often observed. Between attacks paroxysmal outbursts of an epileptic pattern are still liable to occur in the E.E.G. and so help in the diagnosis. Wave and spike complexes, usually associated with petit mal, are the most striking of these patterns. It has been observed, however, that the amount of wave and spike activity in an E.E.G. bears no strict relationship to the liability of clinical petit-mal attacks to develop during that recording; nor does it give any clear indication of the severity or frequency of the attacks at other times (Jewesbury and Parsonage 1949).

Williams (1944a) found characteristic or "larval" epileptic disturbances of the E.E.G. in 27% of epileptics but in none of 650 non-epileptics. Other paroxysmal outbursts, not sufficiently well defined to be included in the first group, occurred in a further 29% of epileptics but in only 0·5% of non-epileptics. Thus, paroxysmal outbursts of all kinds in the E.E.G. were over 100 times as common in epileptics as in non-epileptics.

Williams (1944b) found similar outbursts in 26% of cases of post-traumatic epilepsy. Certain patients, however, whose E.E.G. showed paroxysmal activity after a head injury, did not develop epileptic attacks in a 5-year follow-up. In such cases the E.E.G. is an oversensitive index of the liability to epileptic attacks.

NON-SPECIFIC DYSRHYTHMIAS

In addition to the paroxysmal outbursts in the E.E.G., non-specific dysrhythmias of various kinds may be seen. These vary in amount and in degree and, although commoner in epileptics than in normal persons, have no clear diagnostic significance. They occur in many forms of cerebral abnormality or cortical instability, and are also seen in a minority of normal people. Williams found that, in addition to the 56% of idiopathic epileptics who showed specific paroxysmal changes in the E.E.G., a further 19% showed non-specific dysrhythmia. Thus, the total incidence of abnormality of the E.E.G. in idiopathic epilepsy was 75%. In cases of head injury with and without subsequent fits the corresponding figures were 63% and 60% respectively.

Non-specific dysrhythmias account almost entirely for the abnormalities of the E.E.G. in non-epileptic people. In Williams's series such changes occurred in about 12% of unselected normal persons, in 23% of a group of neurotics, and in 50% of chronic post-traumatic states (post-concussional syndrome). Non-specific dysrhythmias are also seen more often than normally in cerebral disturbances due to toxic and infective conditions, in schizophrenia, in psychopathic states, in behaviour disorders, and in some patients who are subject to frequent faints or migraine. Lennox et al. (1940) found that about 60% of the near relations of epileptics showed some dysrhythmia in the E.E.G. Such dysrhythmias in the E.E.G. of apparently normal people may indicate, as Williams (1941) has put it, "an inborn constitutional defect which may find expression as epilepsy or a behaviour disorder such as constitutional psychoneurosis, psychopathy, or psychosis in the subject himself or his offspring." The E.E.G. changes that tend to be associated with psychomotor epilepsy are often indistinguishable from those of aggressive psychopathy; and, if only non-specific dysrhythmia is found, the E.E.G. is well-nigh valueless in diagnosis.

ADVICE ABOUT MARRIAGE

Advice is sometimes sought by an epileptic about the advisability of marriage and parenthood, and E.E.G. records of both parties to the marriage may be requested. Though paroxysmal activity in the E.E.G. of both might be a deterrent to parenthood, it seems reasonable to discount the presence of any less specific findings.

ABNORMAL E.E.G. IN EPILEPSY

Abnormality of the E.E.G. of epileptics between fits depends on many factors, particularly the type of attacks, the length of the history, the familial tendency, the age of the patient, and his physical state at the time of recording. The older the patient when the attacks first appear, the less likely is the E.E.G. to show any abnormality. Grand mal of late onset is much less likely to produce specific E.E.G. changes than is petit mal in early life. Specific changes in the E.E.G. may be precipitated by opening or closing the eyes, by overbreathing, and by other procedures.

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* Based on a postgraduate lecture given at the North Middlesex Hospital.

Grey Walter (1950), discussing a group of over 2200 patients complaining of fits who had been referred for electro-encephalography (mostly by their own doctors), concluded that in about 70% the cause of fits could be diagnosed clinically without an E.E.G., and that rather less than half of the remainder could be "accurately classified" with the aid of the E.E.G. In this last group cerebral tumour and idiopathic epilepsy were diagnosed in the proportion of about 2 to 1. The E.E.G. diagnosis of cerebral tumour was afterwards confirmed, but one wonders whether a more careful clinical examination before the E.E.G. might not in some cases have led to the same conclusion. It is significant, however, that less than 1 in 1000 of the original cases was diagnosed as epilepsy by electro-encephalography alone. Robinson (1946) found that repeated electro-encephalography increased the probability of correct diagnosis of epilepsy by not more than 5%. Most clinicians would regard this as an overestimate, and the more careful the history-taking and clinical examination the smaller is this figure likely to be.

ACTIVATION OF ABNORMALITIES

Various "activation procedures" have been used in an attempt to evoke specific abnormalities in the E.E.G. Photic stimulation by a light flickering on and off about 20 times a second is commonly used. Grey Walter (1951) states that this leads to a 12% increase in the number of "diagnostic patterns" in the E.E.G. of patients complaining of fits. Unfortunately, comparable diagnostic patterns—and clinical attacks—can be evoked by this means in about 2% of apparently normal people and in about 5% of unstable and psychopathic ones. The reliability of the diagnosis when this technique is used is therefore open to question. Drugs—e.g., leptazol—have also been used as provocative agents; but, although a major seizure and a positive E.E.G. response may be provoked by this means in some epileptics whose ordinary E.E.G. shows no abnormality, positive results may also be given by non-epileptics. It has been impossible to find a dose high enough to provoke a fit in most epileptic patients and yet insufficient to do so in some normal persons. Hutchinson (1951) investigated 100 patients whose routine E.E.G. showed no abnormality; 36 of these were regarded clinically as epileptics and 64 as non-epileptics. The latter group included 10 hysterics. Injections of leptazol produced a positive response in the E.E.G. in 30 (83%) of the epileptics and in 13 (20%) of the non-epileptics.

Just as electrical convulsion therapy can produce fits in non-epileptic persons, so the various pharmacological activating procedures may provoke seizures and specific E.E.G. changes in patients who have never previously had a fit. The overlap between susceptible non-epileptics and relatively unsusceptible epileptics in this type of test tends to confuse rather than to clarify the issue in the doubtful clinical case.

COMPARISON OF EPILEPTICS AND NON-EPILEPTICS

Although a comparison of the E.E.G.s of a large number of epileptics with those of a large number of normal people shows far more abnormal records in the former group, the fact is more of statistical interest than of diagnostic value in any individual case. Too much emphasis can be laid on minor irregularities; and, in the case of high-voltage slow rhythms seen on overbreathing, it is important to know both the age of the patient and his blood-sugar level at the time. Hypoglycaemia and alkalosis particularly favour the development of such delta activity. Brazier et al. (1944) found that delta waves occurred in the third minute of h ventilation in nearly all normal controls if the b sugar level was sufficiently lowered. In 38% of n adults delta waves occurred at non-fasting blood-s levels of 100-130 mg. per 100 ml. In 11% of the no adults delta waves still developed in the third mi if the blood-sugar level was raised above 130 mg. 100 ml. Some workers regard this as a critical le and Heppenstall (1944) considers that instability of th E.E.G. on hyperventilation for three minutes at blo sugar levels above 130 mg. per 100 ml. much incre the probability that the patient is an epileptic.

In the first few years of life the resting E.E.G. is unstable and contains so much slow activity that it never "normal" by adult standards. In childhood a adolescence the E.E.G. still tends to be unstable and t show slow rhythms, particularly in the theta range. I adult life the E.E.G. is less likely to show irregularit as age advances. Sensitivity to overbreathing is al less common in old than young people. Of epilepti (between seizures) the percentage showing abnormalit declines to about 40% at about the age of 30, and t 10% at about the age of 50 (Walter 1950). All the facts have to be taken into account in assessing th significance of any E.E.G.

INCIDENCE OF ABNORMAL E.E.G. IN NORMAL PEOP

There is general agreement that the incidence of a "abnormal" E.E.G. in normal people is between 10% and 15% (Gibbs et al. 1943, Greenblatt 1944, Hoef 1945, Rosson and Gordon 1947, Williams 1951). It seem necessary, however, to describe more accurately su forms of instability as are found, and to take accou of blood-sugar levels at the time of the test so as t make clearer what variations may be expected amo normal people.

I have recently investigated the E.E.G. of 120 norma medical students, aged 20–30. 30 had very flat o unstable alpha rhythm. Beta rhythm was seen in a and was well marked in 21. Theta waves were prese in 30 of the resting records, and in 8 of these they we quite well marked. Theta waves developed on ove breathing in 13 other cases. No delta waves or bilater synchronous outbursts occurred before overbreathing nor were any isolated sharp waves or epileptic feature seen. In 31 cases (26%) medium-voltage to high-voltag delta waves developed on overbreathing, and these we well marked in 23. If one were to take the strictes possible standard of stability or normality—i.e., stab well-marked alpha rhythm, no undue beta or the activity, and no delta activity, even on overbreathing only 58 (just under 50%) of the group would fulfil su criteria. The clinical insignificance of minor non-speci variations in the E.E.G. is thus emphasised, and it becom exceedingly hard to draw the line between what i within the normal range of variation and what is abnorm Criteria of abnormality drawn up in 1945 by the E.E.G Society * are not particularly helpful; but, where r absolute distinctions exist, argument over the out limits of normality is unprofitable.

The blood-sugar was estimated in all the norm students at the time of electro-encephalography. Th average level was exactly the same (103 mg. per 100 ml in the 31 who developed high-voltage slow waves durin overbreathing as in the remaining 89 who did no Raising the blood-sugar level in the susceptible grou however, led to the complete disappearance of the sl waves in all but 3 cases. This varying susceptibility normal people to the state of the blood-sugar furth illustrates that the degree of instability of the E.E.G. to be measured rather on a sliding scale than on a basis which attempts to divide E.E.G. strictly into norm and abnormal.

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* See appendix IV in Electroencephalography. Edited by J. D. Hill and G. Parr. London, 1950.

INCIDENCE OF ABNORMAL E.E.G. IN EPILEPTICS

he E.E.G. of 130 patients who undoubtedly had pathic epilepsy were also studied. A much less strict ndard being used than that adopted for the normal dents, the E.E.G. was regarded as abnormal in 65%. is figure is comparable with that of other workers, standards of abnormality are naturally liable to jective variation.

No estimate of the incidence of E.E.G. abnormality in lepsy is of much value unless it takes into account age of the patient and the nature of the attacks e table).

BSERVATIONS ON 130 CASES OF IDIOPATHIC EPILEPSY

—	100 patients aged over 20 (av. 36)	30 patients aged 11–19
nical incidence of pure petit mal —i.e., without grand mal	1 in 10 cases (approx.)	1 in 3 cases
idence of wave and spike complexes in E.E.G.	3%	11 (37%)
E.G :		
features	34%	20 (67%)
rhythmia only ..	25%	6 (20%)
.. .. ..	41%	4 (13%)

Although the totals are small, the division into age-oups illustrates the higher "normality-rate" in the E.G. of the older group. The younger group has a uch higher proportion of specific E.E.G. abnormalities, d this is to a large extent due to the higher incidence pure petit mal and wave and spike patterns in patients ged less than 20.

CONCLUSION

Many of these statements have become clichés to orkers in electro-encephalography and to most clinical eurologists. The general practitioner, among others, owever, is naturally less conversant with the limitations f the E.E.G. Unless he is aware of the inconstancy of he findings both in epileptics and in normal people e is apt to believe that an E.E.G. can decide the diagnosis a doubtful case of epilepsy. The layman often has natural desire for graphic proof of epilepsy for medico-egal purposes. It cannot be too strongly emphasised, owever, that the best evidence of epilepsy is still to be btained from a careful history from the patient and ye-witnesses of the attacks.

SUMMARY

Perhaps the most interesting achievement of the E.E.G. n relation to epilepsy has been the light that it has hrown on the inherent tendency to epilepsy and allied disorders in people who have never had a fit.

The incidence of various types of dysrhythmia in the E.E.G. of epileptic and non-epileptic people is discussed. Many undoubted epileptics have an E.E.G. indistinguishable from those of normal people.

Instability of the E.E.G. is particularly liable to be en in young people, and some apparently normal eople develop delta waves on overbreathing if their lood-sugar level is rather low.

The degree of disturbance of the E.E.G. in epileptics epends largely on the nature of the epileptic attack nd the patient's age. There is no strict relationship etween the extent of the E.E.G. changes and the frequency f clinical attacks.

The finding of normal rhythms or non-specific dyshythmia in the E.E.G. is of little diagnostic help, and may erely confuse the issue in the case of the patient with doubtful history of epilepsy.

The likelihood of finding an E.E.G. pattern diagnostic f idiopathic epilepsy in a patient whose fits start omparatively late in life is slight. Unfortunately, this just the sort of case where the E.E.G. is specially in demand and where pathognomonic features would be most helpful.

In cases of head injury followed by alleged epilepsy the E.E.G. cannot always provide a dogmatic answer about the nature of the attacks. Nor can it be relied on to indicate whether fits will or will not develop.

When an epileptic seeks advice on marriage and parenthood, it is sometimes recommended that the proposed partner should also undergo electro-encephalography. Both are reassured if this is normal; but, if a non-specific dysrhythmia is discovered in each, an unhappy element of uncertainty may be introduced. It is considered that anything other than paroxysmal dysrhythmia should be discounted in such cases.

Specific E.E.G. changes and epileptic attacks can be induced in some apparently normal people by special "activating procedures." Perhaps those who are sensitive to hypoglycæmia, "flicker," or leptazol have a less stable cortical rhythm, and are therefore more liable to develop epilepsy or allied disorders than their fellows. But to regard such people clinically as potential epileptics is clearly unjustifiable.

It is emphasised to the over-credulous that the E.E.G. is no easy short cut to the diagnosis of epilepsy. The most reliable evidence about the nature of attacks is a careful history obtained from the patient and eye-witnesses.

REFERENCES

Brazier, M. A. B., Finesinger, J. E., Schwab, R. S. (1944) *J. clin. Invest.* 23, 313.
Gibbs, F. A., Gibbs, E. L., Lennox, W. G. (1943) *Arch. Neurol. Psychiat.* 50, 111.
Greenblatt, M. (1944) *Amer. J. Psychiat.* 101, 82.
Heppenstall, M. E. (1944) *J. Neurol. Neurosurg. Psychiat.* 7, 112.
Hoefer, P. F. A. (1945) *In* Brock's The Basis of Clinical Neurology. 2nd ed., Baltimore; p. 260.
Hutchinson, J. T. (1951) *Proc. R. Soc. Med.* 44, 325.
Jewesbury, E. C. O., Parsonage, M. J. (1949) *J. Neurol. Neurosurg. Psychiat.* 12, 239.
Lennox, W. G., Gibbs, E. L., Gibbs, F. A. (1940) *Arch. Neuro Psychiat.* 44, 1155.
Robinson, L. J. (1946) *J. nerv. ment. Dis.* 104, 486.
Rossen, R., Gordon, M. (1947) *Dis. nerv. System*, 8, 373.
Walter, W. G. (1950) *In* Hill, J. D. N., Parr, G. Electroencephalography. London; p. 250.
— (1951) *Proc. R. Soc. Med.* 44, 315.
Williams, D. (1941) *J. Neurol. Neurosurg. Psychiat.* 4, 257.
— (1944a) *Brain*, 67, 10.
— (1944b) *J. Neurol. Neurosurg. Psychiat.* 7, 103.
— (1951) *In* Feiling, A. Modern Trends in Neurology. London; p. 583.

PANCREATIC ENZYME ACTIVITY IN DUODENAL CONTENTS OF CHILDREN WITH A TYPE OF KWASHIORKOR

M. D. THOMPSON
M.D. Birm., M.R.C.P.
MEMBER OF THE STAFF OF
MEDICAL RESEARCH COUNCIL

H. C. TROWELL
M.D. Lond., F.R.C.P.
SPECIALIST PHYSICIAN,
UGANDA MEDICAL SERVICE

From Mulago Hospital and the Department of Medicine, Makerere College, Kampala, Uganda

THE malnutritional state in children which was called kwashiorkor in West Africa (Cicely Williams 1933) has now been described in most tropical countries. Conditions described in reports from Africa, the Caribbean area, tropical America, India, Malaya, Indo-China, the Philippines, and Fiji appear so closely related to kwashiorkor that they are regarded by many as the same (Trowell 1949).

Although it is not a clearly defined condition, particularly in the early stages, the principal features are hair and skin changes, œdema, low serum-albumin, diarrhœa, subnormal weight, anæmia, and occasionally signs of vitamin-B deficiencies. These occur in variable combinations, but hair changes, œdema with weight loss, and diarrhœa are noted by many observers in a high proportion of cases.

The ætiology has not yet been fully established, but many regard the condition as due to protein deficiency.

There does not seem to be any reason to attribute it to gastro-intestinal infection; diarrhœic cases do not commonly show cellular exudate in the stool, and pathogenic bacteria are seldom isolated. Although many cases in Uganda also have malaria or hookworm infection, kwashiorkor occurs in regions where these infections are unknown, such as Fiji (Manson-Bahr 1951) and Durban (Walt, Wills, and Nightingale 1950). Hence such infections cannot account for the condition, though they may perhaps accentuate it.

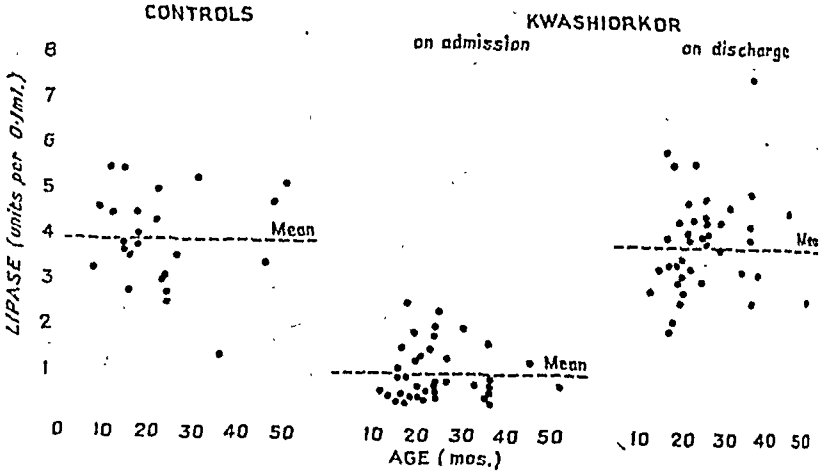

Fig. 2—Maximum concentration of lipase in duodenal contents of same groups as in fig. 1.

Certain features of kwashiorkor suggests that failure of digestion or absorption or both may play a part in its full development. The diarrhœa is frequently associated with bulky unformed stools in which large particles of undigested food are often seen. Although this condition is sometimes seen in stools from healthy African children and must be considered in relation to the nature of the dietary intake, it is so common a feature of kwashiorkor that it has been regarded as evidence of digestive failure. This idea is supported by the fact that many children take an adequate caloric intake for normal growth and yet fail to gain weight. Excessive fat has been reported in the stools by several observers, although no quantitative studies have been reported. Davies (1948, 1950) has consistently found pancreatic changes at necropsies on children dying from this condition, and regards the loss of zymogen granules in the pancreas as a constant change. Similar changes in the pancreas at necropsy have been described by Waterlow (1948), Véghelyi (1948), Hartz (1949), Stransky and Dauis-Lawas (1950), and Manson-Bahr (1951).

Whereas clinical observations suggested interference with digestion or absorption in kwashiorkor, histological evidence indicated that the disorder might be pancreatic in origin. The present investigation was undertaken to determine pancreatic function, in established ca of the type of kwashiorkor seen in Uganda, by estimati of the pancreatic enzyme activity in the duoden contents.

MATERIALS AND METHODS

Diagnostic Criteria

For the purposes of this investigation the criteria "established kwashiorkor" were taken as pitti œdema, without obvious renal or cardiac cause, chang in the hair, and subnormal weight. In all the childr *in this series the hair was scanty, soft, and* unusuall straight, besides showing varying degrees of browne In addition, most of the children presented a variab combination of the other features characteristic of th condition. Skin changes included hyperpigmentatio and peeling, with raw weeping areas in the flexures over sites of pressure. This change was particularly w marked in the groins and axillæ, and also in the fol produced by the œdema at the ankles, neck, and wrist In many children wasting was apparent in the no œdematous parts, or when the œdema had disappeare Some children appeared to have normal amounts of su cutaneous fat. Diarrhœa was prominent feature in 85% of th children, but less than 25% these showed any evidence cellular exudate in the stool Malaria was *present in at* leas 56%, and hookworms in 47% The number of worms remove by treatment varied from 2 t 818, *and only Necator american* has been detected. Anæmia, wi hæmoglobins ranging from 2·8 12·32 g. per 100 ml., was pres and the severe degrees occurr only in association with malari or heavy hookworm infectio Out of 23 cases in which *it* wa possible to estimate serum protein the highest levels wer *5·9 g. per 100 ml. as total* pro tein and 2·9 g. per 100 ml. albumin.

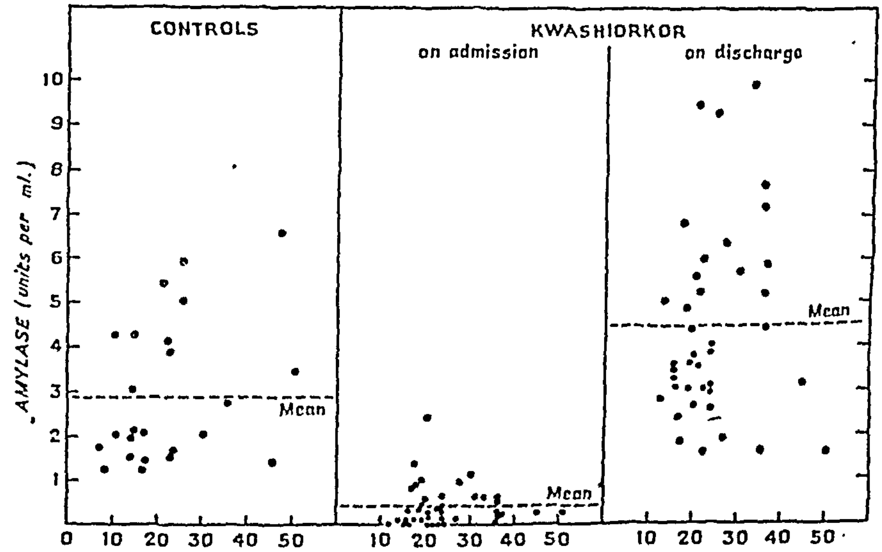

Fig. 1—Maximum concentration of amylase in duodenal contents of 24 control children and of 40 children with kwashiorkor firstly within five days of admission, and secondly when convalescent. The mean values for each group are shown in dotted lines.

The sigma limits are not shown, since they are calculated on the assumption of a symmetrical

Cases

40 children with kwashiork whose ages ranged from 12 to months (mean 24·6, s.d. 8· were the subjects of the ma part of this investigation, and further 10 *(aged* 12–58 month

é intubated on admission only. All 59 fulfilled the ve-mentioned diagnostic criteria for kwashiorkor.

4 children admitted to the ward with other con- ions, who had normal hair and no œdema, acted as trols. The mean age of this group was 23·7 months ige 9–51 months, S.D. 11·95).

estigational Procedure

)n the day of the investigation a dose of potassium mide and chloral hydrate was substituted for the 1 breakfast of porridge. Duodenal intubation was ried out with a radio-opaque tube, the progress and ition of which were checked by X rays. Samples of itents were withdrawn from the second or third part the duodenum by aspiration with an all-glass syringe. e specimens were stored on ice and examined the same y.

Lipase was estimated in ml. of *N*/10 sodium hydroxide uired to neutralise the acid produced from 1 ml. of ve oil by 0·1 ml. of duodenal juice in thirty minutes ile shaken at 37°C at pH 8·0 with bile added to a al concentration of 0·5% (Frazer, Sammons, and iompson 1952).

Amylase was measured in units calculated from the iction constant, starch being used as substrate (Ågren d Lagerlöf 1936).

The initial intubation was done within five days of mission to hospital.

eatment

The ward diet consisted of wheat bread, maize porridge, antains, sweet potatoes, or rice, with soups of ground- its or beans. Meat was included two or three times a eek, but was not given in the earlier cases. There was ı official allowance of about $^1/_2$ pint of milk for each ild, but it was difficult to ensure the administration this in the main part of the ward.

Protein supplements were given, to the children with washiorkor, as whole milk (11 cases), double-strength ried skimmed milk (11 cases), 'Cliftol' (extracted milk rotein) (6 cases), or mixtures of skimmed and whole ilk (12 cases). These were given at the rate of 1 or 2 ints a day, and special precautions were taken to see hat the children took their milk. Unfortunately, the ctual amount given to each child was controlled by the uantity that it could be persuaded or forced to take ather than by any standard formula in relation to weight. Benger's food,' which contains a pancreatic extract, vas added to the milk for those children who would not ake milk alone. Those who could not be persuaded to lrink were fed by gastric tube. When vomiting or liarrhœa prevented effective oral feeding, intravenous ›lasma or blood was used, if it was available.

Solid food was only withdrawn in the initial stages of treatment in those children who were unwilling to take it, or who refused their milk if given food as well.

Various glucose and salt mixtures were given intravenously and subcutaneously to children who became dehydrated or refused fluids. Ferrous sulphate, as a mixture, was given to most of the later patients and to all those who were severely anæmic.

Antimalarial therapy was routine, both for children with kwashiorkor and for controls, during the first week, even when blood slides were negative. Hookworms were treated with tetrachlorethylene and oil of chenopodium, immediately when loads were large or anæmia severe, otherwise shortly before discharge from hospital. Respiratory infections were treated with sulphonamides or penicillin; streptomycin or sulphonamides were given to children with diarrhœa even when there was no cellular exudate.

Reinvestigation

Reinvestigation of enzyme activity in duodenal contents was made in 40 convalescent children after treatment for kwashiorkor, and in 1 child who had refused all forms of protein supplement.

Treatment between the initial and final intubations lasted from seven to fifty-one days and depended on the severity of the case on admission, the rate of recovery of weight and general condition, and how long the mother could be persuaded to remain in hospital with the child.

10 convalescent children were not re-examined: 8 ran away before they were considered fit for discharge; and in 2 the attempted intubation failed.

8 children died: 4 within the first week after admission to hospital and before an adequate protein intake had been established; 2 of recurrent infection after they had shown considerable response four weeks after their protein therapy; and 2 after periods of intractable diarrhœa.

Necropsies were performed on 2 of the children who died within the first week after admission and in the 2 who died with intercurrent infections.

FINDINGS

Controls

The concentration of amylase and lipase found in the duodenal contents of each of the control children are shown in figs. 1 and 2 according to the age of the child, and the means and standard deviations in table I. There is a wide variation within this group, but there is no appreciable relation between age and enzyme activity over the age-range studied (coefficient of correlation with age +0·334 for amylase and —0·138 for lipase).

Kwashiorkor

The concentration of amylase and lipase in the duodenal contents of children admitted with untreated kwashiorkor

TABLE I—SHOWING THE MEAN VALUES AND STANDARD DEVIATIONS FOR MAXIMUM CONCENTRATIONS OF AMYLASE AND LIPASE IN DUODENAL CONTENTS AND AGE IN MONTHS FOR 40 CHILDREN WITH KWASHIORKOR ON ADMISSION AND DISCHARGE, 19 CHILDREN WITH KWASHIORKOR EXAMINED ON ADMISSION ONLY, AND 24 CONTROL CHILDREN

—	No. of cases	Amylase (units per ml.)				Lipase (units per 0·1 ml.)				Age	
		On admission		On discharge		Admission		Discharge		Months	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
ontrols	24	2·92	1·62	—	—	3·84	1·04	—	—	23·72	11·95
Treated: Reintubated	40	0·40	0·46	4·33	2·12	1·0	0·57	3·88	0·99	24·57	8·7
Including:											
(*a*) Whole milk	11	0·32	0·45	4·59	2·30	1·21	0·58	4·05	1·11	23·82	10·6
(*b*) Skimmed milk	11	0·55	0·64	4·19	2·06	1·0	0·70	3·47	0·79	21·54	5·3
(*c*) Milk protein	6	0·33	0·43	4·07	1·68	1·08	0·66	3·78	1·42	26·83	12·8
(*d*) Mixed milks	12	0·37	0·26	4·36	2·43	0·75	0·25	4·13	0·79	26·92	6·9
Not reintubated	10	0·50	0·45	—	—	1·30	0·66	—	—	27·7	11·92
Died	8	0·53	0·81	—	—	0·81	0·56	—	—	20·0	6·51
Untreated: Reintubated ..	1	0·05	—	0·1	—	1·0	—	0·9	—	—	—

The mean admission values for the 19 children not re-examined do not differ significantly from the admission levels of the 40 who were reintubated after treatment. The mean levels of both amylase and lipase for these 40 are very significantly lower on admission than the control levels, the probability of their occurrence as random fluctuations being less than 0·001.

On discharge, the mean lipase level is almost exactly equal to that of the control group, and the amylase level is just significantly above the control-group level; the probability of their occurrence as random fluctuations being less than 0·01.

TABLE II—MEAN INCREASES IN MAXIMUM AMYLASE AND LIPASE CONCENTRATION IN THE DUODENAL FLUID OF GROUPS OF CHILDREN RECEIVING DIFFERENT FORMS OF MILK SUPPLEMENT

Treatment	No. of cases	Amylase (units per ml.)	Lipase (units per 0·1 ml.)
Whole milk	11	4·27	2·85
Skimmed milk ..	11	3·64	2·47
Milk protein	6	3·73	2·68
Mixture	12	3·99	3·38
All	40	3·93	2·88

All of these increases are very highly significant, the probability of their occurrence as random fluctuations being below 0·001. There is no significant difference between the means in the three groups.

is shown in figs. 1 and 2 for each of the 40 children who were subsequently re-examined when convalescent.

The means and standard deviations are given in table I, which also includes the mean admission values in the 19 children who were not examined a second time.

There was a marked depression of enzyme activity, both of amylase and of lipase, in children admitted with kwashiorkor, compared with the levels found in controls and in the same kwashiorkor patients when convalescent.

In the last columns of figs. 1 and 2 are shown the concentration of amylase and lipase found in the duodenal contents of these same 40 kwashiorkor patients when convalescent. The means and standard deviations are shown in table I, and the increases in lipase and amylase levels during treatment in table II and figs. 3 and 4. There is a very significant increase in the activity of both enzymes after treatment.

Response to Different Forms of Milk

In tables I and II the mean values for concentration of the enzymes and the increases for each group receiving a different form of milk supplement are separated, and in figs. 3 and 4 the increase for each child is shown according to the duration of treatment. There is no significant difference between the mean increases in each group.

Effect of Treating Infections Without Giving Milk Supplement

One of the children included in figs. 1 and 2 received no additional protein during the first ten days in hospital. Amylase and lipase were 0·05 and 1·0 unit respectively on admission and 0·1 and 0·9 unit at the end of this period. After fourteen days on milk, these values rose to 3·5 and 4·8 units respectively. In the one child who ran away after refusing every form of protein supplement the amylase remained at 0·1 and the lipase fell from 0·9 to 0·4 unit during eighteen days in hospital, although his infections had been energetically treated.

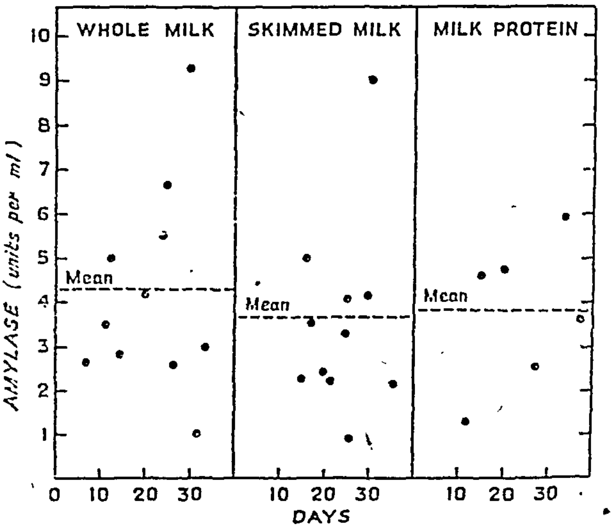

Fig. 3—Increases in maximum amylase concentration in duodenal contents of children with kwashiorkor treated with whole milk (11), skimmed milk (11), or 'Cliftol' extracted milk protein (6). The means for each group are shown in dotted lines.

Histopathology

At necropsy the pancreases of the 2 children who died within a few days of their initial intubation showed loss of cytoplasm in the acinar cells of the pancreas so that the appearance was that of almost solid nuclei. There was some collapse of acinar structure with an increase in interacinar fibrous tissue. The pancreases of the 2 children who died with intercurrent infection after receiving four weeks of high-protein feeding appeared histologically normal.

DISCUSSION

These findings show that there is a significant depression of lipase and amylase concentration in the duodenal contents of children with established kwashiorkor of the type described here. The range of values for concentration of enzyme activity in the controls is wide, owing largely to the number of variables involved in the technique of collection. Duodenal contents are a mixture of pancreatic, biliary, gastric, and small-intestine juices, although with careful sampling it is possible to obtain fluid which is predominantly pancreatic juice (usually mixed with bile). Although no figures for trypsin were obtained, lipase and amylase (in any one sample) showed similar trends, and the parallel concentration of pancreatic enzymes has been demonstrated (Babkin 1950). It may therefore be inferred that the levels found represent pancreatic enzyme activity.

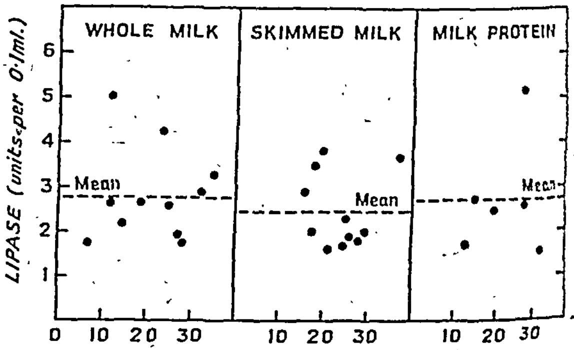

Fig. 4—Increases in maximum lipase concentration in duodenal contents of same groups as in fig. 3.

Enzyme activity returns to normal levels during a period of weeks (one to seven in this series) in which therapy consists of milk or milk-protein supplements to the standard adult diet, with the treatment of any active infection. Reports of decreased digestive enzymes in the duodenal contents of children suffering from conditions which are similar to, and perhaps identical with, kwashiorkor have been published from Brazil (Carvalho et al. 1947) and Hungary (Véghelyi 1948). Véghelyi noted that recovery of enzyme activity took place when the children were given milk, which had been unobtainable at the onset of the condition. His reports give no factual data of levels obtained. The effects of milk or milk protein in promoting clinical recovery have been observed by all who have tried it (Altmann 1948, Trowell 1949, Walt et al. 1950, Van der Sar 1951). Milk has probably been used because it is a convenient and easy means of giving large amounts of protein to small sick children. Other forms of treatment—e.g., with vitamin supplements—have met with only sporadic and unsubstantiated successes.

Temporary absence of pancreatic activity in duodenal contents, such as we have found in this type of kwashiorkor r, could be due to intestinal or pancreatic causes. No zyme activators (analogous to enterokinase for ypsinogen-trypsin) are required for amylase or lipase, d the addition of bile in vitro does not increase the ase activity in these cases. There is no evidence to ggest a generalised enzyme inhibition.

The most likely cause of the absence of enzyme activity a failure of an active juice to reach the duodenum. ilure to secrete normal amounts of enzyme might be ie to the absence of the normal hormonal and neural imulating mechanism. Although there is no suggestion this, the possibility could be examined by testing the sponse to pancreozymin, secretin, and parasympathetic ugs. There is no histological evidence of gross pan- eatic disease which might prevent the access of normally rmed juice to the duodenum and there are no changes milar to those observed in cystic fibrosis of the pancreas.

Histopathological studies of pancreatic tissue in itreated fatal cases show an absence of zymogen anules, and, possibly more significant, an absence of toplasm around the nuclei. As the nuclei retain their ormal staining qualities, this seems unlikely to be ue to post-mortem change. In 2 of our children who ied with intercurrent infections after they had shown msiderable response to four weeks' high-protein therapy, ie pancreas appeared histologically normal. This iggests that these histological changes may be reversible -a view which would be in keeping with the functional covery of the pancreatic activity in other children of is series. It has lately been shown that pancreatic sions in rats can be caused by interfering with methio- ine metabolism by feeding ethionine (Farber and Popper 950, Goldberg et al. 1950). The reversible depression f pancreatic enzyme activity produced in chicks on yptophane-deficient diets (Russell et al. 1950) is rther evidence that it is possible to interfere with ancreatic function by specific deficiency of protein omponents of the diet. It is generally recognised that he diet of children developing kwashiorkor has an xtremely low protein content, consisting mainly of egetables which are particularly poor in protein. heir total protein intake therefore may well be deficient, specially as protein requirements relative to body- veight and calorie requirements are very high at this age. n all cases in which serum-proteins have been estimated here has been evidence of severe hypoproteinæmia.)ther factors, such as recurrent infections and parasites, nay also increase the turnover of available protein.

Our experience shows that in this type of kwashiorkor he low pancreatic enzyme activity of untreated cases ecovers rapidly if enough protein is absorbed. It seems easonable to suppose that deficiency of pancreatic nzyme may interfere with digestion in the small intes- ine, and thus reduce absorption of protein. In this way he protein deficiency in the body may be further ggravated. If this is true, it might be useful in severe ases to give predigested protein, digestive enzymes, or parenteral protein.

SUMMARY AND CONCLUSION

1. Pancreatic enzyme activity in duodenal contents was studied (a) in 59 African children suffering from a type of kwashiorkor and (b) in 24 apparently normal African children who were comparable in age and who formed the control group. The presence of œdema, without obvious renal or cardiac cause, hair changes, and subnormal weight were the criteria used for the diagnosis of kwashiorkor.

2. In all the children with kwashiorkor the concentration of amylase and lipase in the duodenal contents was well below normal.

3. This defect was reversed in all children who received a high intake of milk protein and in whom intercurrent infections, if present, were treated.

4. The 2 children with kwashiorkor who did not receive milk protein showed no significant rise of enzyme activity in the duodenum and made no clinical improvement, although their intercurrent infections were treated.

5. The possible cause of this depression of enzyme activity, and its relation to the illness and its treatment are discussed.

Many people have helped in this work. We should like to thank them all, particularly the Director of Medical Services, Uganda, Prof. E. G. Holmes, and Dr. A. W. Williams for facilities and advice; Dr. J. Scott Brown, Mr. Hewlett Parker, and Mr. C. H. J. Wild for their patience and coöperation in the X-ray department; Dr. A. B. Raper and Dr. B. G. Elmes for the pathological investigations; the house-physicians, Dr. L. Musoke and Dr. J. Semambo; and the sisters and nurses of Mulago Hospital. We should also like to thank Professor A. C. Frazer, Dr. H. G. Sammons, and Dr. J. M. French, and other members of the Pharmacology Department of Birmingham University, for their help, and Dr. J. A. H. Waterhouse, of the Department of Medical Statistics, Birmingham, for statistical analysis and advice.

ADDENDUM

Since this paper was prepared, the concentration of trypsin activity in the duodenal contents of 6 children admitted with kwashiorkor, of the type defined above, has been determined. The method used was that of Charney and Tomarelli (1947) involving the colorimetric estimation of the digestion products of a sulphanilamide-azocasein complex. The test was repeated in 3 of the children on recovery.

The concentration of trypsin, amylase, and lipase in the duodenal contents of these children are given in the table below together with those for 1 control child.

—		Trypsin (units per ml.)		Amylase (units per ml.)		Lipase (units per 0·1 ml.)	
		Ad-mitted	Dis-charged	Ad-mitted	Dis-charged	Ad-mitted	Dis-charged
Kwashiorkor	1	4·3	46	0	2·3	0·2	3·6
	2	2·3	53	0·5	3·2	0·2	4·8
	3	5·6	60	0·2	2·7	0·8	4·0
	4	2·3	—	0	—	0·2	—
	5	1·4	—	0	—	0·1	—
	6	9·1	—	0·2	—	0·8	—
Control ..		56	—	2·5	—	3·8	—

These results show that there is a reversible depression of the concentration of trypsin activity in the duodenal contents of a small series of children admitted with kwashiorkor of the type defined in this paper. In these 3 children this finding was associated with changes in amylase and lipase similar to those occurring in the rest of the series considered above. The inference that trypsin is involved in the depression of pancreatic enzyme activity in this type of kwashiorkor therefore appears to be justified.

REFERENCES

Ågren, G., Lagerlöf, H. (1936) *Acta med scand.* 90, 8.
Altmann, A. (1948) *Clin. Proc.*, 7, 32.
Babkin, B. P. (1950) Secretory Mechanism of Digestive Glands. New York.
Carvalho, M., Schmidt, M. M., Pinto, A. G. (1947) *J. Pediat., Rio*, 13, 141.
Charney, J., Tomarelli, R. M. (1947) *J. biol. Chem.* 171, 501.
Davies, J. N. P. (1948) *Lancet*, i, 317.
— (1950) Liver Injury. Transactions of the Ninth Conference, Josiah Macy, Jr., Foundation, New York; p. 151.
Farber, S., Popper, H. (1950) *Proc. Soc. exp. Biol., N.Y.*, 74, 838.
Frazer, A. C., Sammons, H. G., Thompson, M. D. (1952) To be published.
Goldberg, R. C., Chaikoff, I. L., Dodge, A. H. (1950) *Proc. Soc. exp. Biol., N.Y.*, 74, 869.
Hartz, Ph. H. (1949) *Docum. neerl. ind. Morb. trop.* 1, 41.
Manson-Bahr, P. E. C. (1951) *Trans. R. Soc. trop. Med. Hyg.* 44, 555.
Russell, W. C., Taylor, M. W., Lane, I. W. (1950) *Fed. Proc.* 9, 368.
Stransky, E., Dauis-Lawas, D. F. (1950) *Ann. Pædiatr.* 174, 226.
Trowell, H. C. (1949) *Trans. R. Soc. trop. Med. Hyg.* 42, 417.
Van der Sar, A. (1951) *Docum. neerl. ind. Morb. trop.* 3, 25.
Véghelyi, P. V. (1948) *Acta pædiatr., Stockh.* 36, 128.
Walt, F., Wills, L., Nightingale, R. P. (1950) *S. Afr. med. J.* 24, 920.
Waterlow, J. C. (1948) *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 263; p. 29.
Williams, C. D. (1933) *Arch. Dis. Childh.* 8, 423.

CHEMOTHERAPY FOR STAPHYLOCOCCUS AUREUS IN BURNS

E. J. L. LOWBURY
M.A., B.M. Oxfd

ELIZABETH TOPLEY
M.D. Lond.

A. M. HOOD
F.I.M.L.T.

From the Medical Research Council's Burns Research Unit, Birmingham Accident Hospital

CONTROLLED prophylactic and therapeutic trials on burns in this unit have shown the clinical and bacteriological value of locally applied polymyxin E against *Pseudomonas pyocyanea* and some coliform bacilli, and of local penicillin against *Streptococcus pyogenes* (Jackson et al. 1951a and b). Clark et al. (1943) found that local application of penicillin to burns was often followed by the elimination of *Staphylococcus aureus*; this organism, however, has continued to be prevalent on burns in spite of routine penicillin prophylaxis and other measures which were associated with a lower incidence of *Strep. pyogenes* (Colebrook et al. 1948).

We describe here studies on the action of local penicillin, of local dibromopropamidine, and of aureomycin on the colonisation of burns by *Staph. aureus*. The evidence for the bacteriological value of different chemotherapeutic agents was in the main derived from controlled trials in which patients, on admission to the burns unit, were allocated to one or other of the treatment groups. General or local treatment with aureomycin was shown to have bacteriological value. The emergence of aureomycin-resistant strains during oral chemotherapy was examined with the aid of bacteriophage typing of a wide range of staphylococci from burns.

METHODS

Data for this investigation were provided by patients treated in the Birmingham Accident Hospital burns unit between November, 1948, and January, 1952. The treatment of these cases, including dressing of inpatients in an air-conditioned room by a strict no-touch technique, was in most respects identical with that described by Colebrook and his colleagues (Colebrook et al. 1948, Colebrook 1950).

Sampling and Culture Methods

Burns were sampled with moistened swabs for bacteriological examination at all dressings and operations, or daily if the burn could not be covered with dressings. Swabs were inoculated on 10% horse-blood-agar (containing 2% or 6% agar), on a cetrimide selective medium for isolation of *Ps. pyocyanea*, and, after August, 1949, in Robertson's cooked-meat medium, which was subcultured to blood-agar after overnight incubation at 37°C.

For neutralisation of penicillin transferred on swabs to media, blood-agar was made up with 10 units of penicillinase per ml. An attempt was made to use lecithin, as recommended by Elson (1944), for the neutralisation of dibromopropamidine in media; dried egg or lecithin (5 mg. per ml.) in broth was no more effective in neutralising added dibromopropamidine than was cooked-meat medium, and its use in a solid medium proved impracticable. Occasionally growth was inhibited on blood-agar at the primary inoculation site of swabs from burns treated with dibromopropamidine as long as six days previously. In assessing the results of dibromopropamidine treatment, therefore, reliance was placed entirely on the results of subculture from cooked-meat medium, which neutralised 0·2 ml. of a 0·15 g. per 100 ml. solution of dibromopropamidine (the strength used in the cream applied to burns).

Special methods for neutralising aureomycin were not used, because it had already been reported (Paine et al. 1948) that aureomycin quickly loses potency on incubation at 37°C in 10% horse-blood-agar, and we had found that zones of inhibition of aureomycin-sensitive organisms round discs containing aureomycin up to 10 μg. per ml. were overgrown when plates were reincubated overnight at 37°C. For three weeks all the plates were reincubated for a further forty-eight hours in case aureomycin delayed the appearance of colonies of staphylococci, but this did not happen.

During the first month of the trial of local aureomycin each swab was inoculated in two tubes of cooked-meat medium, one of which received a drop containing about [illegible] viable aureomycin-sensitive staphylococci. Heavy growth of *Staph. aureus* was detected in all the tubes which received the additional inoculum.

All varieties of colony on incubated blood-agar plates were picked for morphological examination and subcultured to small areas of blood-agar (6% agar). Loopfuls of the growth of all the gram-positive cocci in these areas were inoculated into 0·5 ml. quantities of 10% plasma-broth, which were incubated at 37°C for eighteen to twenty-two hours (Williams and Harper 1946). Tests showing either complete or partial coagulation were called coagulase-positive. The designation *Staph. aureus* or staphylococcus was used for all coagulase-positive gram-positive cocci.

Sensitivity Tests

All the strains of *Staph. aureus* were tested for sensitivity to penicillin. Until December, 1949, a plate dilution method was used (Williams 1949). The same strains were tested for penicillinase production by incubating 2 ml. of a twenty-four-hour broth-culture with 1 ml. of an aqueous solution of penicillin 100 units per ml. for an hour, and transferring the mixture to Heatley cylinders on an agar plate previously seeded with Oxford staphylococcus. Absent or reduced zones of inhibition round the cylinders after overnight incubation of the plates were taken to indicate penicillinase production. Since December, 1949, we have tested penicillin sensitivity by the multiple-streak ditch-plate method (Barber 1947a) using blood-agar plates with ditches containing 10 units of penicillin per ml. of agar. By penicillin-resistant we mean resistant by the ditch-plate method, and therefore probably penicillinase-producing. By penicillinase-producing *Staph. aureus* we mean strains actually tested for penicillinase production.

From August, 1949, to January, 1950, all the strains of *Staph. aureus* were tested for sensitivity to dibromopropamidine by an agar-plate dilution method, the doubling dilutions used being from 0·3 to 5·0 μg. per ml.

From September, 1950, all the strains of *Staph. aureus* were tested for sensitivity to aureomycin by the ditch-plate method, using 10 μg. of aureomycin per ml. of agar in the ditch. From September to November, 1950, and again in April, 1951, all the strains resistant by this method—i.e., producing a zone of inhibition 2 mm. or more narrower than that of the Oxford staphylococcus—were also tested by a tube dilution method (Topley et al. 1951). The terms "aureomycin-sensitive" and "aureomycin-resistant" refer here to the results of the ditch-plate test, resistant strains being inhibited in the tube test by minimal concentrations of aureomycin that range from 0·08 to 4·00 μg. per ml. (about 4–200 times as resistant as the Oxford staphylococcus). The concentration of aureomycin is stated in terms of a weighed amount of aureomycin hydrochloride (Lederle) from a capsule which contained additional excipients and flavouring agents.

Bacteriophage Typing

The method described by Wilson and Atkinson (1945) was used, with slight modifications, including the use of 1[illegible] additional bacteriophages, and preliminary screening by pooled phages (Hood 1952). Undiluted phages were not used. Strains of *Staph. aureus* from burns, and sometimes from nose and throat of burned patients, were typed during some of the trials of penicillin, dibromopropamidine, and aureomycin, and during several periods, including a month (April, 1951) in which different aureomycin-resistant staphylococci were isolated. Strains isolated from cooked-meat medium have recently not been typed, because of the reported alteration of type specificity when staphylococci of different phage types are grown in the same fluid medium (Smith 1948).

Assay of Antibiotic in Exudate

Exudate from the burns of patients receiving aureomycin and their controls were tested for the presence of aureomycin by the blotting-paper disc method, with *Bacillus cereus* and an aureomycin-sensitive penicillin-resistant strain of *Staph. aureus* as indicator organisms (Topley et al. 1951).

LOCAL PENICILLIN

The 'Lanette wax' cream (Colebrook 1950) applied to burns at each dressing contained penicillin 400–10[illegible] nits per g. The very limited value of this cream n preventing or treating the colonisation of burns y *Staph. aureus* was defined in controlled trials on 52 npatients (Jackson et al. 1951b) and 258 outpatients blished). The high incidence of staphylococci on burns treated with penicillin can be appreciated from the results of the controlled trial of aureomycin (table I). All the patients were receiving local penicillin as a routine, but among patients not receiving aureomycin 76% of sites yielded *Staph. aureus* after the third day. The failure of local penicillin was in large part due to the high incidence of penicillin-resistant staphylococci. It was clear, however, that even in the absence of penicillinase-producing staphylococci local penicillin applied at about weekly intervals was not very effective in preventing or treating the colonisation of burns by penicillin-sensitive staphylococci.

Penicillin was seldom applied more often and in greater strength. When 9 burn sites colonised by penicillinase-producing staphylococci were treated with local penicillin 10,000 units per g. every other day, they all continued to yield staphylococci during the next seven days. Only three sites colonised by penicillin-sensitive staphylococci were so treated, and in each case the staphylococci were not isolated between the fourth and seventh days. These results may indicate the failure of local penicillin, 10,000 units per g. to control colonisation of burns by penicillin-resistant staphylococci.

Since, however, local penicillin 1000 units per g. is of value in preventing the colonisation of burns by *Strep. pyogenes* (Jackson et al. 1951b), it should be used as a routine application to burns. It is therefore worth emphasising our finding that, when local penicillin is being used as a routine, added infections with ward strains of penicillinase-producing staphylococci of the 6/47 group are extremely common. This finding was obtained by testing the penicillin resistance of all staphylococci isolated from burns, and by phage-typing all these staphylococci during different months and during a controlled trial. The details of our experience are essentially similar to those already reported in other hospitals (Barber 1947b, Barber and Whitehead 1949, Forbes 1949, Rountree and Thomson 1949).

LOCAL DIBROMOPROPAMIDINE

Dibromopropamidine isethionate was introduced for clinical trial in 1948 by May & Baker Ltd. before aureomycin and the other newer antibiotics had been described. The results of careful in-vitro tests of different organisms made it clear that gram-positive cocci were usually more sensitive than gram-negative bacilli to dibromopropamidine (Wien et al. 1948), and there have been claims that it is clinically valuable in the local treatment of wounds (Kohn and Cross 1948) and burns (Arden 1949, Champion and McDowall 1949).

Preliminary trial of dibromopropamidine on areas of industrial dermatitis (11 patients) colonised with penicillinase-producing *Staph. aureus* or *Strep. pyogenes* suggested that it may be of clinical value, and that it often eliminated or reduced the incidence of staphylococci when applied every day in a concentration of 1·5 g. per 100 g. In 7 of 23 (30%) burn sites *Staph. aureus* present initially was absent from swabs taken at dressings done between the fourth and the seventh days after the start of local treatment with dibromopropamidine (0·15–0·5 g. per 100 g.). Although no controlled trial was made, the finding suggests that in some cases dibromopropamidine was of value in eliminating *Staph. aureus* from burns. Dibromopropamidine in concentrations of 0·5 g. per 100 g. or more sometimes caused smarting on application to burns.

From Sept. 1 to Nov. 14, 1949, most burns were dressed as a routine with dibromopropamidine isethionate 0·15 g. per 100 g. in a carbowax base, which during this period was substituted for the local penicillin cream (400 units per g.) in routine use. Dibromopropamidine solution (0·15 g. per 100 ml.) was used as a spray for exposed burns. The results of this trial period indicated no significant change in the incidence of staphylococcal colonisation of burns, but there was a fall in the proportion of staphylococci which were resistant to penicillin.

The reason for discontinuing the use of dibromopropamidine as a routine treatment for burns was clinical. It seemed in 3 patients that the slough of full-thickness skin-loss separated more slowly than is usual with penicillin cream. This made it necessary to excise rather than to strip the granulations at operations and led to unnecessary hæmorrhage. It proved more difficult to differentiate full-thickness from partial-thickness skin-loss, but this might have become easier with more experience. Daily photographs and skin biopsies on 2 patients suggested that the epithelisation of very deep burns with partial-thickness skin-loss might have been delayed (D. M. Jackson, personal communication). The

TABLE I—CONTROLLED TRIAL OF ORAL AUREOMYCIN

(Numbers of burns yielding *Staph. aureus*)

First swab from burn (1–3 days)	Chemotherapy	No. of burns	Presence or absence of *Staph. aureus*														
			Days 4–5			Days 6–7			Days 4–7				All dressings after 3rd day			
			+	−	% +	+	−	% +	+	−	% +	Significance tests	+	−	% +	Significance tests
Staph. aureus present	Aureomycin	24(4)	6(0)	9(1)	40	4(2)	5(1)	44	8(2)	12(2)	40	$\chi^2 = 7{\cdot}1$, $P < 0{\cdot}01$	10(4)	14(0)	42	$\chi^2 = 6{\cdot}2$, $P < 0{\cdot}02$
	No aureomycin ..	22(1)	11(0)	2(0)	85	9(0)	0(0)	100	15(0)	2(0)	88		18(1)	4(0)	82	
Staph. aureus absent	Aureomycin	36(11)	2(0)	15(0)	12	4(4)	15(5)	21	6(4)	23(5)	21	Not significant	19(6)	17(5)	53	Not significant ($\chi^2 = 3{\cdot}6$).
	No aureomycin ..	45(8)	5(0)	8(0)	38	5(0)	12(6)	29	10(0)	17(6)	37		34(3)	11(5)	76	
No swab	Aureomycin	10(4)	1(0)	3(1)	25	1(0)	2(0)	33	1(0)	5(1)	17	Not tested	7(1)	3(3)	70	Not tested
	No aureomycin ..	14(2)	6(0)	1(0)	86	4(1)	0(1)	100	8(1)	1(1)	89		13(1)	1(1)	93	
Total	Aureomycin	70	9	27	25	9	22	29	15	40	27	$\chi^2 = 11{\cdot}9$, $P < 0{\cdot}001$	36	34	51	$\chi^2 = 13{\cdot}2$, $P < 0{\cdot}001$
	No aureomycin ..	81	22	11	66	18	12	60	33	20	62		65	16	80	
Total excluding face burns	Aureomycin	54	2	20	9	62	16	79	6	34	15	$\chi^2 = 14{\cdot}5$, $P < 0{\cdot}001$	25	29	46	$\chi^2 = 14{\cdot}2$, $P < 0{\cdot}001$
	No aureomycin ..	71	15	9	63	13	10	57	25	18	58		57	14	80	
Total plus burns grafted on admission	Aureomycin	89	9	29	24	15	28	35	21	48	30	$\chi^2 = 7{\cdot}5$, $P < 0{\cdot}01$	47	42	53	$\chi^2 = 9{\cdot}7$, $P < 0{\cdot}01$
	No aureomycin ..	92	22	11	67	19	19	50	34	27	56		70	22	76	

Figures in parentheses refer to burns grafted on admission.

toxicity of dibromopropamidine to human phagocytes and guineapig skin (Wien et al. 1948) was a further reason for preferring penicillin. It was therefore decided to discontinue the use of dibromopropamidine as a routine application for burns, and no controlled trial was made.

ORAL AUREOMYCIN

The value of aureomycin as a chemotherapeutic agent for staphylococcal infections has been widely reported (Nichols and Needham 1949; Arnold 1950, Long 1950, *Altemeier and Culbertson 1951)*. When the trials were started in this unit, 124 stains of *Staph. aureus* from burns and stock strains of 28 bacteriophage types of the organism were tested and shown to be sensitive to aureomycin 0·16 µg. per ml.; 145 strains being sensitive to 0·04 µg. per ml. or less (Topley et al. 1951). Topley et al. (1951) also showed that aureomycin can be detected at concentrations of about 1–10 µg. per ml. in burn exudate of patients receiving aureomycin by mouth. We therefore decided to use oral rather than local aureomycin to assess its effectiveness in eliminating and in excluding *Staph. aureus* from burns. It should be emphasised that, as described above, the concentrations of aureomycin refer to the weight of an impure product.

Controlled Prophylactic Trial (86 patients, 43 treated, 43 controls)

Between August and November, 1950, all the patients admitted to the adult male burns ward were allocated on a random basis to aureomycin-treated or control groups. Patients with odd hospital numbers were given aureomycin by mouth for their first six days in hospital, while patients with even hospital numbers did not receive aureomycin. The dose was 1 capsule (250 mg.) of aureomycin hydrochloride six-hourly. Covered burns of patients in both groups were dressed, whenever possible, on the fifth or sixth day—before auremoycin was discontinued in cases of the treated series. *Both treated* and control patients received the routine application of penicillin cream 1000 units per g. at their initial dressing, and severely burned patients were also given parenteral penicillin 300,000–1,000,000 units a day.

A preliminary assessment of the trial in November, 1950, showed that patients whose burns were not excised and grafted on admission acquired *Staph. aureus* less often when aureomycin was given than when it was not given; on grafted burns, by contrast, added *Staph. aureus* was about equally common in patients of the treated and the control series, possibly because a skin graft prevented the aureomycin from reaching the organisms. Patients whose burns were excised and grafted on admission were therefore not included in an extension of the trial from November, 1950, to January, 1951. During this period patients aged more than 1 year in the women's and children's ward were included in the trial. Children aged less than 10 years were given a smaller dosage of aureomycin (25 mg. per kg. body-weight daily), the younger children having it dissolved in orange-juice.

Results of Controlled Prophylactic Trial

Table I shows the number of burns in treated and control series from which *Staph. aureus* was isolated on at least one occasion four or more days after admission. Most of the results under the column headed "Days 4–5" in the treated group were from patients still receiving aureomycin. The column headed "All dressings after 3rd day" provides evidence of the over-all effect of aureomycin given for a few days only. Results from patients whose burns were excised and grafted on admission are separately entered in parentheses after the results from other patients in the trial.

46 burns were colonised by *Staph. aureus* during the first three days. In this group *Staph. aureus* was isolated after the third day from 18 out of 22 (82%) burns of patients not treated with aureomycin, but from only 10 out of 24 (42%) burns of patients who received aureomycin ($\chi^2 = 6{\cdot}2$, $P < 0{\cdot}02$). At every period shown in the table the proportion of burns from which *Staph. aureus* could be isolated was higher in the control than in the treated series.

TABLE II—CONTROLLED TRIAL OF ORAL AUREOMYCIN
(Numbers of burns yielding aureomycin-sensitive and aureomycin-resistant *Staph. aureus* on all dressings after third day*)

Sensitivity of staphylococci to aureomycin	Treatment	Staph +	Staph −	Total	% +	χ^2	P
Sensitive	Aureomycin	23	47	70	32·9	7·75	<0·01
	No aureomycin ..	46	35	81	56·8		
Resistant	Aureomycin	14	56	70	20·0	No significant difference	
	No aureomycin ..	15	66	81	18·5		

* Staph + refers to burns yielding, in one group, aureomycin-sensitive staphylococci and, in the other, resistant staphylococci only: the remaining sites being described as Staph −. Staphylococci from six sites were not tested for sensitivity to aureomycin.

81 burns were free from *Staph. aureus* during the first three days. In this group also the proportion of burns from which *Staph. aureus* could be isolated was consistently lower in the aureomycin-treated than in the control series, but the difference was smaller than it was in the burns initially colonised by *Staph. aureus*, and did not reach the level of statistical significance.

From these results it appears that aureomycin had a therapeutic effect, leading to the elimination of some staphylococci when they were initially present in a burn, and, probably, a prophylactic effect, by which burns initially free from *Staph. aureus* were protected against colonisation by the organism. When the bacteriological results from all the burns, including those from which no swabs were taken during the first three days, are pooled, there is a more significant difference between the proportion of burns in the aureomycin and control series which had staphylococci after the third day (aureomycin series 36 out of 70 (51%); control series 65 out of 81 (80%); $\chi^2 = 13{\cdot}2$, $P < 0{\cdot}001$). The difference in the pooled results is still significant if the burns grafted on admission are included, and more pronounced after deducting results for face burns, which are exposed and therefore more likely to be contaminated.

Table II shows the incidence of *Staph. aureus* after the third day in burns not grafted on admission, classified in two groups according to the sensitivity of strains to aureomycin by the ditch-plate method. It will be seen that the incidence of aureomycin-resistant staphylococci was unaffected by oral aureomycin, and the incidence of sensitive strains was significantly lower in cases treated with aureomycin than in the controls.

There was no evidence of any prophylactic or therapeutic effect of aureomycin on other organisms isolated from burns during the trial. *Ps. pyocyanea* was isolated after the third day from 39 out of 70 (56%) burns in the aureomycin series, and from 50 out of 81 (62%) of the control burns, grafted burns being excluded in each case. There is no significant difference in these proportions. Added infection with β-hæmolytic streptococci did not occur in either aureomycin or control series during the first week in hospital. Coliform bacilli were present after the third day in a larger proportion of burns treated with aureomycin—55 out of 70 (79%)—than in burns of the control patients—40 out of 81 (49%). This difference was significant ($\chi^2 = 12{\cdot}5$, $P < 0{\cdot}001$).

Therapeutic Use of Aureomycin

26 patients with *Staph. aureus* in their burns were treated at varying times after admission, for periods from a few days to six weeks, with oral aureomycin either

because their burns were colonised by *Strep. pyogenes* or for clinical reasons—e.g., graft failure or local inflammation in the presence of penicillinase-producing staphylococci, pneumonia, or pyrexia of unknown origin. Table III shows the bacteriological results of such therapy in terms of the isolation of staphylococci after 4–7 days and 8–28 days from the beginning of therapy. A high proportion of sites initially colonised by *Staph. aureus* continued to yield this organism during and after aureomycin therapy. The table shows, however, that burns colonised by aureomycin-resistant strains of *Staph. aureus* did not lose them, whereas 6 out of 25 (24%) of those swabbed between the fourth and seventh days which were initially colonised by aureomycin-sensitive staphylococci or strains of unknown sensitivity had lost the organism in that time.

In most of the burns still colonised by aureomycin-sensitive *Staph. aureus* during and after aureomycin therapy the numbers of staphylococci isolated were smaller than at the beginning of treatment, and in a few patients this was associated with definite clinical improvement—e.g., resolution of local inflammation and fall in temperature.

Aureomycin in Exudate

Disc samples were normally taken from the burns of treated and control patients in the aureomycin trial and of patients receiving aureomycin for clinical reasons. Exudate from 10 control cases never produced zones of inhibition round the discs. Approximately 1–5 µg. aureomycin per ml. was demonstrated in the exudate of 16 out of 18 (89%) burns of aureomycin-treated patients from whom discs were taken within twenty-four hours of discontinuing aureomycin. It was sometimes possible to detect aureomycin two or three days, but never (0 out of 6 burns) more than three days, after aureomycin was discontinued. In several patients whose burns yielded *Staph. aureus* during aureomycin therapy the burn was too dry to be tested for aureomycin.

Effect of Aureomycin on Nasal Carriage of Staph. aureus

Daily nose swabs were taken from aureomycin-treated and control patients during the first week in hospital. *Staph. aureus* was isolated after 4–8 days from 23 out of 30 (77%) aureomycin-treated and from 22 out of 26 (85%) control patients. Strains of *Staph. aureus* resistant to aureomycin by the ditch-plate method but sensitive to aureomycin 0·16 µg. per ml. in the tube test appeared (usually after the fourth day) in 8 out of 23 (35%) aureomycin-treated and 4 out of 22 (18%) control patients carrying *Staph. aureus*.

All of 25 strains of *Staph. aureus* isolated from the first nose swab taken after admission were sensitive to aureomycin. In 8 out of 20 (40%) aureomycin-treated patients sensitive strains were replaced during the first eight days by resistant strains, whereas in 11 control patients only 1 sensitive strain was replaced by a resistant strain. Staphylococci of the 6/47 phage group were more often isolated from later swabs than from those taken on admission. It is therefore clear that oral aureomycin 1 g. a day was not effective in eliminating nasal *Staph. aureus*, and the nose may prove a source of aureomycin-resistant staphylococci when oral aureomycin is used in the ward.

Sensitivity Tests during Controlled Trial of Aureomycin (from August, 1950, to January, 1951)

The proportion of *Staph. aureus* strains resistant by the ditch-plate test was greater in the burns of aureomycin-treated patients—91 out of 222 (41%)—than in those of control patients—64 out of 273 (23%). The difference was significant ($\chi^2 = 17{\cdot}1$, $P < 0{\cdot}001$).

Emergence of Resistant Strains (from August, 1950, to April, 1951)

The resistant control used for the ditch-plate test was one of the most resistant strains of *Staph. aureus* isolated between July and September, 1950. Towards the end of 1950, strains began to be isolated which were on the routine tests much more resistant, often showing no zone of inhibition and growing across the aureomycin ditch. In 1951 an increasing number of such strains was noticed. In April, 1951, tube dilution sensitivity tests were done on all the strains resistant by the ditch-plate test, and all the strains of *Staph. aureus* were tested for phage type. Of 514 strains isolated from the burns of 73 patients during that month 303 (59%) were resistant by the ditch-plate method, and 227 of these were more resistant than any strain tested in the earlier period, 119 requiring a minimal concentration of 4·0 µg. of aureomycin per ml. to inhibit growth. No strains were resistant to aureomycin 4·0 µg. per ml. Of the 29 patients from whose burns these more resistant staphylococci were isolated in April, 1951, 21 had never received aureomycin. Moreover, 25 of them had burns on exposed or imperfectly covered sites, which were therefore likely to acquire infection in hospital.

Phage-types of Staphylococci

Table IV shows the results of bacteriophage typing of all the strains of *Staph. aureus* isolated from burns in April, 1951. It can be seen that many of the staphylococci were lysed by several phages at their test dilution; hence a considerable number of combinations or patterns of phage-types were present. It was usual to find more than one type or pattern represented in repeated swabbings of the same burn.

The results of bacteriophage typing are of interest in relation to the emergence of aureomycin-resistant strains. Aureomycin resistance increased without any change in phage-type in staphylococci from 3 out of 8 patients who, during April, 1951, were receiving or had just received aureomycin. In 2 of these the staphylococcus was of type 75, and in 1 it was of type 47/75. This finding might have been caused either by an increase in the aureomycin resistance of the staphylococci carried by these burns or by added or coincident infection with resistant staphylococci of the same phage-type.

TABLE III—PATIENTS RECEIVING AUREOMYCIN FOR CLINICAL REASONS

(Numbers of burns yielding *Staph. aureus*)

Initial *Staph. aureus*	No. of burns	*Staph. aureus* 4–7 days after starting aureomycin						*Staph. aureus* 8–28 days after starting aureomycin					
		Aureomycin-resistant	Aureomycin-sensitive	Sensitivity unknown	Scanty growth*	No growth	Burns swabbed	Aureomycin-resistant	Aureomycin-sensitive	Sensitivity unknown	Scanty growth*	No growth	Burns swabbed
Aureomycin-resistant ..	12	7	1	0	1	0	9	9	2	0	0	0	11
Aureomycin-sensitive ..	17	4	4	1	2	3	14	7	4	1	1	1	14
Sensitivity unknown ..	12	5	1	1	1	3	11	5	0	3	2	1	11

* Growth in fluid medium (cooked meat) only.

Evidence that resistance may occur in a number of phage-types of *Staph. aureus*, but that certain types are in this unit today more likely than others to be resistant to aureomycin, is shown in table IV. As in previous months, most of the staphylococci from burns were members of the 6/47 group, which contains most of the penicillinase-producing strains. Some of the staphylococci in this group which were lysed by certain phages were less commonly resistant to aureomycin than strains lysed by other phages. For example, 46 out of 51 strains lysed by phage 7, and all of 12 strains lysed by phage 75A, were sensitive to aureomycin. By contrast only 20 out of 102 strains lysed by phage 76, and 15 out of 57 strains lysed by phage 31B, were sensitive to aureomycin. Almost all of these strains were resistant to penicillin.

Further study is required to show whether the routine use of aureomycin induces a change in the distribution of phage-types, and resistance within each phage-type, comparable to the change associated with the routine use of penicillin in burns. Meanwhile it is of interest that a wide range of staphylococcal types were resistant to aureomycin after it had been used for several months.

PRELIMINARY NOTE ON TRIAL OF LOCAL AUREOMYCIN

A controlled trial, which is still in progress, has been undertaken to assess the value of local aureomycin as a chemoprophylactic and therapeutic agent on burns. The application consisted of a cream containing aureomycin 2 mg. (adjusted to pH 6·0) and penicillin 1000 units per g. of lanette-wax base. Patients treated by the covered method were divided into two groups, one with odd, and one with even, hospital numbers. At every dressing the cream containing aureomycin was applied to burns in one group, and the other group received penicillin cream only. Patients who had skin grafts on admission were excluded, because all grafts were dressed with tulle gras.

The bacteriology of swabs taken from burns at all dressings up to the time of grafting was investigated, and the incidence of *Staph. aureus* in the two groups has been compared after three months of the trial. Of 88 burns in 26 patients treated with aureomycin cream 52 (59%) had *Staph. aureus* at some time after the second day and before the application of skin grafts; 64 out of 85 (75%) burns in 26 patients receiving the control penicillin cream had *Staph. aureus* during the same period. A significantly smaller proportion of burns treated with aureomycin cream was therefore found to be colonised by the organism ($\chi^2 = 4{\cdot}51$, $P < 0{\cdot}05$). The effect was on the staphylococci sensitive to aureomycin by the ditch-plate test. These strains were present in 7 out of 88 (7·9%) burns treated with aureomycin, and in 24 out of 85 (28%) burns treated with the control cream ($\chi^2 = 16{\cdot}36$, $P < 0{\cdot}001$). In contrast, local aureomycin appeared to have no bacteriological effect on aureomycin-resistant staphylococci.

TABLE IV—BACTERIOPHAGE TYPES OF *Staph. aureus* FROM BURNS IN APRIL, 1951

Bacteriophage type or pattern	Penicillin-sensitive staphylococci		Penicillin-resistant staphylococci	
	Aureomycin-sensitive	Aureomycin-resistant	Aureomycin-sensitive	Aureomycin-resistant
Predominantly aureomycin-resistant:				
75	—	—	6	25
31B/75	—	—	—	10
76	—	—	7	49
31B	—	—	12	27
47/75/76	—	—	8	29
47/75	—	—	13	53
47/31B/75	—	—	—	2
47/31B/75/76 + ..	—	—	—	1
6/31B	—	—	—	1
47/31B	—	—	—	1
47/76	—	—	—	1
7/47/53A/54/76 + ..	—	—	1	2
7/47/53A/54 + ..	—	—	—	1
53	—	—	—	1
47 + ...	—	—	2	3
Predominantly aureomycin-sensitive:				
7	—	—	33	2
7/47/53A/54/75 + ..	—	—	5	—
7/53A + ...	—	—	2	—
7/53A/54 + ...	—	—	1	—
42B	—	—	1	—
31B/42B	—	—	2	—
75A	—	—	1	—
7/53A	2	—	—	—
75/75A	—	—	8	—
47/53A/54/75/75A/76 +	—	—	2	—
7/47/53A/54/75A ..	—	—	1	—
6/47	—	—	1	—
47/53/75	—	—	3	1
77	—	—	1	—
47/53A/54/75	—	—	1	—
7/47D	—	—	1	—
3C/51	2	—	—	—
42E	1	—	—	—
Neither predominant:				
Not typable	40	—	11	48
75/76	1	—	—	1
31B/76	—	—	1	1
Not tested	14	—	27	44
Total	60	—	151	303

DISCUSSION

Colebrook et al. (1948) emphasised that we still cannot control the colonisation of burns by *Staph. aureus*. Although the prospect for the future is better, today at least as many burns as in 1948 are becoming colonised by staphylococci, almost all of them resistant to penicillin. In our studies the limitations of routine treatment with local penicillin have been defined by controlled trials, and dibromopropamidine, which was used as the routine application for ten weeks, appeared to be no better than local penicillin in its bacteriological effect. Aureomycin 1 g. daily by mouth for five or six days was shown by controlled trial to be of definite bacteriological value, mainly in eliminating *Staph. aureus* present on admission, but also probably in reducing the incidence of added infection with this organism. Nevertheless half of the aureomycin-treated patients acquired *Staph. aureus* at some time in hospital. Better results might have been expected if aureomycin treatment had been continued throughout the patient's stay in hospital, but the risk of toxic effects, notably diarrhœa and vomiting, make such prophylactic administration impracticable. Another disadvantage found during oral aureomycin therapy was the emergence of relatively resistant strains (see below). Oral aureomycin appeared to have no effect on the colonisation of burns by these relatively resistant strains. The value of such treatment would therefore be expected to diminish as the proportion of aureomycin-resistant staphylococci in the ward increases.

Higher concentrations of aureomycin can be obtained by applying it locally to the burn. Studies in progress show that local application of aureomycin cream causes a significant reduction in the incidence of *Staph. aureus*, but this appears to be largely, if not entirely, the result of action against aureomycin-sensitive strains.

The present evidence suggests that the main obstacle to the control of staphylococcal colonisation of burns by antibiotics is the absence of an antibiotic to which staphylococci do not acquire resistance.

In spite of the limited value of local penicillin, local dibromopropamidine, and aureomycin in the routine control of the staphylococcal colonisation of burns, there is probably a place for the use of each drug. Penicillin is, in our opinion, the best local application because of its proven value in preventing streptococcal colonisation (Jackson et al. 1951b), a fact that outweighs the risks of an increasing incidence of penicillinase-producing staphylococci. The risks of skin sensitisation to penicillin have not proved serious in this unit.

Dibromopropamidine has the clinical disadvantages described above, which limit its use in burns. Evidence suggests that, given in concentrations which may be toxic to a burn and applied every other day or daily, it may sometimes eliminate *Strep. pyogenes* (Jackson et al. 1951b) and *Staph. aureus* but not *Ps. pyocyanea* (Bull et al. 1948, Jackson et al. 1951a), from skin lesions. Possibly for small unhealed or overgranulating areas which are not to be grafted dibromopropamidine may sometimes be valuable. Clinical impression supports this view, which is not easily defined by controlled trial.

Aureomycin locally or by mouth is shown to have bacteriological value for burns colonised by aureomycin-sensitive *Staph. aureus*, but in its use the risks of the emergence of aureomycin-resistant strains should be borne in mind. There is a case for reserving the oral administration of aureomycin for patients with clinical complications due to penicillin-resistant staphylococci.

It has not been found practicable to define the clinical importance of a potential pathogen in burns, unless an effective method of chemoprophylaxis was applied throughout the patient's period in hospital (Jackson et al. 1951a). Information on this question is one of the objects of the trial of local aureomycin at present in progress. There are, however, a few occasions when staphylococcal colonisation of burns produces dramatic clinical changes, and then effective treatment with aureomycin provides evidence not only of its clinical value but also of the probable pathogenicity of the aureomycin-sensitive organism. Jackson (1951) reports the successful treatment of septic thrombophlebitis with oral aureomycin.

Data suggesting that aureomycin resistance may be developed during aureomycin therapy are now coming to light (Altemeier and Culbertson 1951). In this unit increased resistance to aureomycin has been found in a considerable proportion of staphylococci since the introduction of aureomycin therapy, and cross-infection by these resistant strains is common and probably of clinical importance. Aureomycin-treated cases have shown a significantly higher incidence of resistant staphylococci than those not receiving aureomycin, and the appearance of more resistant organisms during the administration of aureomycin has often been noted. Even with the aid of phage-typing, however, it is still uncertain whether this change is always due to added infection by resistant staphylococci or is sometimes due to an increased resistance of staphylococci already colonising a burn. The fact that the same phage-type of staphylococcus isolated from the same burn has been sensitive on one day and resistant on a later day during aureomycin therapy strongly suggests the development of resistance in the burn, especially as a similar degree of resistance can be induced in vitro (L. Hurst, personal communication); it could also, however, be explained as an added or coincident infection by a resistant staphylococcus of the same phage-type as the strain previously isolated. The resistance of burn staphylococci did not always increase in cases receiving aureomycin even for periods of more than fourteen days; on the other hand, it sometimes appeared in patients who had received aureomycin for only five or six days.

Since the introduction of aureomycin in this unit, added infection with aureomycin-resistant staphylococci has taken place both in burns and in noses of patients not receiving aureomycin. Six months after the introduction of aureomycin, over half the patients with staphylococci in their burns yielded strains resistant to aureomycin. Probably the spread of these strains would have been materially less if all the patients could have been isolated in cubicles.

SUMMARY

Local penicillin 400–1000 units per g. was of limited value in controlling the colonisation of burns by penicillin-sensitive *Staph. aureus*. Penicillin-resistant strains were predominant among inpatients. Local penicillin is, however, recommended as the routine local application to burns because of its value in preventing colonisation by *Strep. pyogenes*.

Local dibromopropamidine isethionate 0·15 g. per 100 g. did not appear more effective than penicillin in controlling staphylococcal colonisation of burns. The clinical disadvantages of applying this agent as a routine are briefly described.

The value of aureomycin 0·25 g. six-hourly for five or six days from admission was tested in a controlled trial on 86 patients. 36 out of 70 (51%) burns of aureomycin-treated patients yielded *Staph. aureus* at some dressing after the third day, in contrast to 65 out of 81 (80%) burns of control patients ($\chi^2 = 13{\cdot}2$, $P < 0{\cdot}001$). This effect was apparently confined to the aureomycin-sensitive strains of *Staph. aureus*.

Aureomycin 1–2 g. a day was given to 26 patients because of either clinical infection or streptococcal colonisation. If the *Staph. aureus* was sensitive by the ditch-plate test, there was often a considerable reduction in numbers and sometimes complete elimination of the organism.

Aureomycin 1–2 g. a day by mouth appeared in burn exudate in concentrations often varying from 0·5 to 5·0 μg. per ml.

Oral aureomycin was of no value in eliminating *Staph. aureus* from the noses of patients in a burns ward. Aureomycin-resistant *Staph. aureus* appeared in the noses of 8 out of 23 aureomycin-treated and 4 out of 22 control patients.

During the nine months after aureomycin was first introduced into the burns unit there has been a considerable increase in the incidence of *Staph. aureus* moderately resistant to aureomycin, and an increase in the degree of resistance of such strains. All the strains have been inhibited by aureomycin 4 μg. per ml., but this concentration is not often reached in the exudate of patients treated with oral aureomycin.

The evidence suggests that most of the patients with burns colonised with aureomycin-resistant strains have acquired the organism by cross-infection.

A study in progress on the routine use of local aureomycin cream has shown a significant reduction in the incidence of aureomycin-sensitive *Staph. aureus* in burns.

We wish to thank the Antibiotics Clinical Trials (Non-Tuberculous Conditions) Committee of the Medical Research Council for supplies of aureomycin; May & Baker Ltd. for dibromopropamidine isethionate; Dr. R. E. O. Williams for the supply of phages and for help in phage-typing; Prof. J. R. Squire and Dr. J. P. Bull for advice; Mr. W. Gissane, clinical director of the Birmingham Accident Hospital, for permission to carry out the clinical research; Sister M. Nicholls, Sister E. Hitchens, Mr. L. Hurst, Miss E. R. McNab, Miss S. Timms, Miss G. Peierls, and Miss B. Over for assistance; and Dr. Leonard Colebrook for his interest and encouragement.

REFERENCES

Altemeier, W. A., Culbertson, W. R. (1951) *J. Amer. med. Ass.* 145, 449.
Arden, G. P. (1949) *Brit. J. plast. Surg.* 2, 109.
Arnold, G. G. (1950) *J. Pediat.* 36, 647.
Barber, M. (1947a) *J. Path. Bact.* 59, 373.
— (1947b) *Brit. med. J.* ii, 863.
— Whitehead, J. E. M. (1949) *Ibid*, ii, 565.
Bull, J. P., Ross, W. P. D., Squire, J. R., Topley, E. (1948) *Lancet*, ii, 747.
Champion, A. H., McDowall, A. (1949) *Brit. J. plast. Surg.* 2, 57.
Clark, A. M., Colebrook, L., Gibson, T., Thomson, M. L., Foster, A. (1943) *Lancet*, i, 605.
Colebrook, L. (1950) A New Approach to the Treatment of Burns and Scalds. London.
— Duncan, J. M., Ross, W. P. D. (1948) *Lancet*, i, 893.
Elson, W. O. (1944) *J. biol. Chem.* 154, 717.
Florey, H. W., Chain, E., Heatley, N. G., Jennings, M. A., Sanders, A. G., Abraham, E. P., Florey, M. E. (1949) Antibiotics. London.

References continued overleaf

THE ABILITY OF THE NORMAL KIDNEY TO CONSERVE POTASSIUM

PAUL FOURMAN
M.D. Lond., M.R.C.P.
MEDICAL TUTOR, UNIVERSITY OF OXFORD MEDICAL SCHOOL

SINCE flame photometry has made it easy to measure potassium accurately in biological fluids (Hald 1951), deficiency of potassium has been more often recognised (Danowski 1949, Darrow and Pratt 1950), mainly in diabetic acidosis, diarrhœa, and after operation. It probably occurs more often than can be ascertained from serum-potassium levels alone (Tarail and Elkinton 1949).

One might expect the kidney to conserve potassium when the body is deficient in potassium, as it conserves sodium when the body is deficient in sodium; but patients who lack potassium may continue to excrete potassium in their urine (Tarail and Elkinton 1949). For this several explanations have been put forward:

(1) Excretion of potassium in the face of deficiency occurs in acidosis, when stores of base are drawn on to enable the kidney to excrete an excess of acid radicles; and in alkalosis, when the kidney possibly excretes K ions in place of H ions *that are to be conserved (Berliner et al. 1951).*

(2) Increased excretion of potassium results from adrenal overactivity. Since patients who have become deficient in potassium are ordinarily ill for other reasons, continued urinary loss of potassium could in them be attributed to the adrenal overactivity of stress (Eliel et al. 1950, Fourman et al. 1950).

(3) There may normally be a minimal obligatory loss of potassium in the urine. It has been suggested that the *urinary concentration of potassium may not fall below that* in the plasma (Tarail and Elkinton 1949), though low urinary concentrations of potassium have been reported during *recovery from diabetic acidosis and after protracted vomiting* in children (Atchley et al. 1933, Mateer et al. 1949).

TABLE I—DETAILS OF THREE METABOLIC BALANCE EXPERIMENTS

—	Diet (m.eq. per day)			Resin			Fæcal potassium (m.eq. per day)	Recovery period (days)
	Na	K	Ash	Form	Amount (g.)	Days		
PF(1)	223	38·0	60·0, alkaline (Na as citrate)	H	60 90	8 8	46 55	8
PF(2)	181	31·2	46·0, alkaline (Na as mixture of organic salts)	NH_4	60 90	8 8	72 79	12
K A-W	212	35·7	24·0, acid (Na as NaCl)	NH_4	60 90	8 4	59 76	0

Potassium deficiency has been little studied in normal persons. It is difficult to induce potassium deficiency without starvation, because most foods contain potassium. Starvation in itself leads to potassium excretion because of tissue breakdown; further, it may constitute an injury that stimulates the adrenals. Thus it is not clear to what extent normal persons not exposed to stress can conserve potassium in response to deficiency of potassium.

We have induced potassium deficiency in two normal persons receiving an adequate diet by giving a cation-exchange resin ('Zeo-Karb 225') with the diet. The insoluble resin takes up cations (mainly Na and K) in the bowel and gives off in exchange either H or NH_4 ions according to the form in which the resin is given. If the exchange is complete, each gramme of resin gives off 2·5 m.eq. of H or NH_4 ion. This amount of NH_4 is equivalent to 128 mg. (about gr. 2) of NH_4Cl. The resin therefore leads to a metabolic acidosis. In our experiments recovery from the acidosis was rapid after the administration of resin was stopped, whereas recovery from the potassium depletion was slow. Hence the effect of potassium deficiency on the renal excretion of potassium could be studied both during and after the period of acidosis.

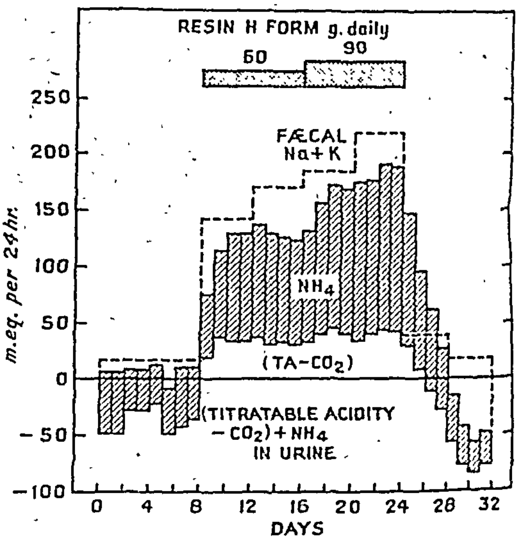

Fig. 1—Effect of cation-exchange resin on urinary acidity and ammonium, and on fæcal Na and K, in experiment PF (1). Titratable acidity (clear area) is plotted from the zero line. Negative values indicate that the urine was alkaline. Ammonium (hatched area) is plotted up from the values for the titratable acidity. Hence the sum of the two, representing base conserved by the kidneys, is measured from the zero line. The sum of the fæcal Na and K is shown by an interrupted line.

PROCEDURE

Three balance experiments were done on two persons (K A-W and PF). The food for the duration of an experiment was prepared in daily portions at the beginning of the experiment and cooked in the laboratory as required. The diet was thus identical from day to day. After a preliminary period of 12 or more days, the resin was given with meals in a dose of 60 g. daily for 8 days and then 90 g. daily for 4 days in one experiment (K A-W) and for 8 days in two experiments (PF). In the experiments on PF balances were measured for a further 8 and 12 days during the period of recovery (table I). Added Na in the diet was taken not as a condiment but between meals, to avoid Na deficiency. K A-W received added Na as NaCl; the acidosis caused the experiment to be stopped prematurely. PF received Na as organic salts; this helped to mitigate the acidosis. All estimations were done in duplicate at least; and, where the estimations involved ashing, two ashes were prepared. A whole day's cooked diet was analysed three times in duplicate in each experiment. Balances of N, P, Ca, K, Na, and Cl, and the urinary titratable acidity and ammonia were measured, and will be reported in detail. Here are presented those results that have a bearing on the question of renal conservation of potassium. Sodium and potassium were measured with an internal-standard flame photometer.* Urinary

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* I am indebted to Dr. B. McArdle for his help in enabling me to copy an instrument of his design.

DR. LOWBURY AND OTHERS: REFERENCES—*continued*

Forbes, G. B. (1949) *Brit. med. J.* ii, 569.
Hood, A. M. (1952) *J. Hyg., Camb.* (in the press).
Jackson, D. M. (1951) *Brit. med. J.* i, 72.
— Lowbury, E. J. L., Topley, E. (1951a) *Lancet*, ii, 137.
— — — (1951b) *Ibid*, p. 705.
Kohn, F., Cross, C. D. (1948) *Ibid*, ii, 647.
Long, P. H. (1950) *Ibid*, i, 420.
Nichols, D. R., Needham, G. M. (1949) *Proc. Mayo Clin.* 24, 309.
Paine, T. F. jun., Collins, H. S., Finland, M. (1948) *J. Bact.* 56, 489.
Rountree, P. M., Thomson, E. F. (1949) *Lancet*, ii, 501.
Smith, H. W. (1948) *J. Hyg., Camb.* 46, 82.
Topley, E., Lowbury, E. J. L., Hurst, L. (1951) *Lancet*, i, 87.
Wien, R., Harrison, J., Freeman, W. A. (1948) *Ibid*, i, 711.
Williams, R. E. O. (1949) Cited by Florey et al. (1949); p. 202.
— Harper, G. J. (1946) *Brit. J. exp. Path.* 27, 72.
Wilson, G. S., Atkinson, J. D. (1945) *Lancet*, i, 647.

TABLE II—EFFECT OF RESIN ON K BALANCE, SERUM CO_2 AND K, AND URINARY K

Treatment	Day	K A-W Cumulative K balance (m.eq.)	K A-W Plasma CO_2 (m.eq. per litre)	K A-W Serum K (m.eq. per litre)	K A-W Urinary K concentration (m.eq. per litre)	K A-W Urinary K excretion (m.eq. per 24 hr.)	PF(1) Cumulative K balance (m.eq.)	PF(1) Plasma CO_2 (m.eq. per litre)	PF(1) Serum K (m.eq. per litre)	PF(1) Urinary K concentration (m.eq. per litre)	PF(1) Urinary K excretion (m.eq. per 24 hr.)	PF(2) Cumulative K balance (m.eq.)	PF(2) Plasma CO_2 (m.eq. per litre)	PF(2) Serum K (m.eq. per litre)	PF(2) Urinary K concentration (m.eq. per litre)	PF(2) Urinary K excretion (m.eq. per 24 hr.)
Mean control	..	..	28	3·7	7·4	29	..	21	4·0	12·3	38	..	24	4·0	7·7	26
Resin 60 g.	2	−146	20	..	5·8	37	−62	..	..	9·3	28	−110	..	..	6·2	25
	4	−264	..	..	3·8	..	−113	..	..	8·0	23	−213	..	..	5·9	22
	6	−366	19	3·6	2·4	15	−176	..	..	6·3	18	−297	..	..	4·6	17
	8	−452	..	..	1·9	12	−232	17	4·4	5·2	15	−372	..	..	3·7	13
Resin 90 g.	2	−564	..	..	1·9	13	−283	..	..	5·0	15	−461	..	..	3·0	11
	4	−672	12	3·7	1·6	11	−332	..	..	5·0	15	−548	15	2·9	2·8	10
	6	..	..	..	..	..	−408	..	..	4·2	12	−683	..	..	2·8	10
	8	..	..	..	..	..	−483	17	3·0	4·2	12	−817	16	2·8	2·8	10
Recovery	2	..	..	..	..	..	−458	..	..	3·6	7	−814	..	..	3·4	9
	4	..	..	..	..	..	−431	..	..	2·8	7	−805	..	..	2·0	6
	6	..	..	..	..	..	−386	..	..	2·0	6	−770	..	..	1·6	4
	8	..	..	..	..	..	−340	28	3·4	1·8	5	−732	..	..	1·0	3
	10	..	..	..	..	..	..	..	..	..	..	−692	..	..	0·9	3
	12	..	..	..	..	..	..	..	..	..	..	−652	29	2·9	1·1	4

acidity was estimated after the carbonic acid had been quantitatively removed by adding HCl in excess. The urine was then back-titrated with NaOH, phenolphthalein being used as an indicator. Thus titratable acidity $-$ HCO_3 = m.eq. NaOH added $-$ m.eq. of HCl added. Ammonium was measured by formol titration.

RESULTS

The resin took up large amounts of cation in the bowel. Absorption of acid radicles was not affected. As a result acidity and ammonia production increased in the urine. The sum of (titratable acidity $-$ HCO_3) + NH_4 measures the amount of base conserved by the kidney (Albright and Reifenstein 1948). This sum was not quite equal to the increased fæcal loss of cation, and acidosis developed (table II). Early in the recovery period the urinary acidity and NH_4 returned to normal. Fig. 1 illustrates the findings in one experiment (PF[1]).

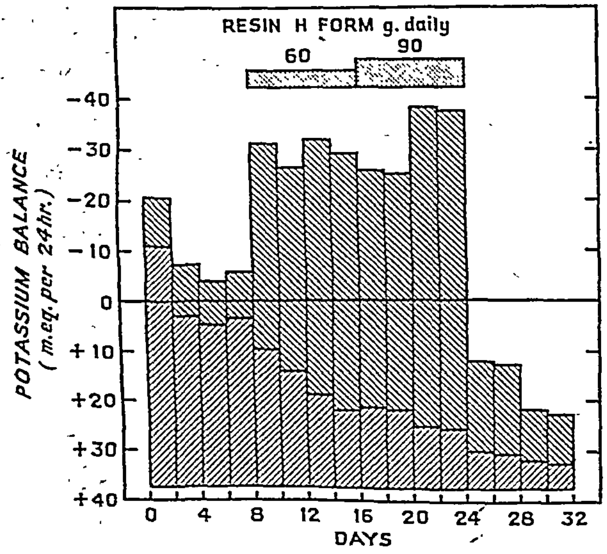

Fig. 2—Effect of cation-exchange resin on potassium balance in experiment PF(1). The intake is plotted downwards from the zero line. The urinary output is plotted upwards from the intake. The fæcal output is plotted upwards from the urinary output. If the sum of the two is less than the intake the positive balance is shown by a clear area below the zero line. If the sum of the two is greater than the intake, the negative balance is shown by a hatched area above the zero line.

With the resin there was some loss of sodium from the bowel, but the subjects of the experiments remained in sodium balance. The loss of potassium from the bowel exceeded the dietary intake (table I), and the negative balance of potassium was aggravated by continued urinary loss of potassium (fig. 2). The total deficit of potassium was 672 m.eq. in K A-W, 483 m.eq. in PF(1), and 817 m.eq. in PF(2). The serum-potassium level did not change in K A-W; it fell in PF. In K A-W the concentration of potassium in the urine fell below the serum concentration while the acidosis was at its height (fig. 3), but K A-W was drinking enormous quantities of water, and the ensuing diuresis may have contributed to the low urine-potassium level. In PF the urine-potassium level fell below the serum-potassium level during the recovery period when the acidosis was receding (figs. 3 and 4).

The data show that, in normal persons, the kidney tubules can reabsorb potassium against a concentration

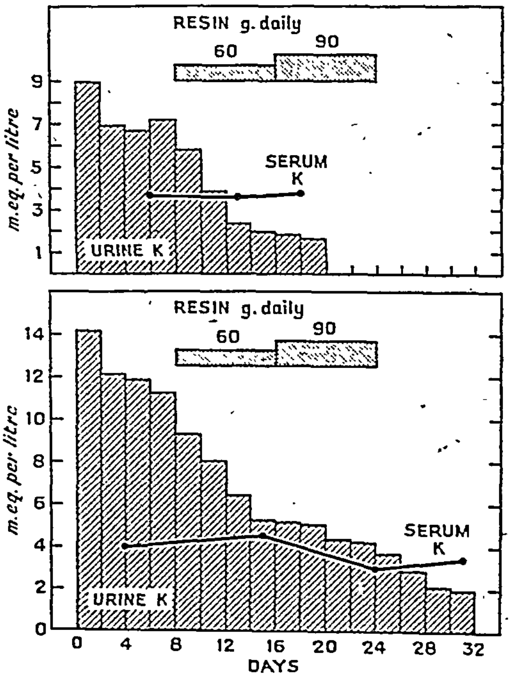

Fig. 3—Comparison of levels of potassium in serum and urine experiments K A-W and PF(1).

gradient, and in certain conditions this may happen even in the presence of acidosis.

DISCUSSION

Tarail and Elkinton (1949) were unable to demonstrate conservation of potassium in normal persons, but their experiments were of short duration. Our results show that renal conservation of potassium can occur, though it takes some days to become established (Mateer et al. 1949, Black 1951), and it may fail in the presence of acidosis.

Since in normal persons the kidney can conserve potassium, there must be a factor in ill people that allows their kidney to lose potassium in the face of potassium deficiency. Many do so though they have no disturbance of acid-base balance. Possibly they do so partly as a result of the adrenal overactivity that accompanies stress. The secretion of glucocorticoids is increased with stre[illegible] cause an increased excretion of [illegible]

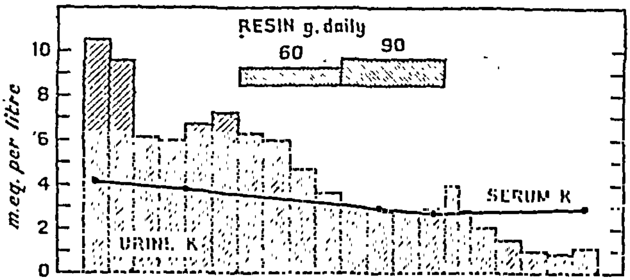

Fig. 4—Comparison of levels of potassium in serum and urine in experiment PF(2).

SUMMARY

Ill people who are deficient in potassium continue to lose potassium in their urine.

Potassium deficiency was studied in two normal persons to determine whether they could conserve potassium.

A negative potassium balance was induced with a cation-exchange resin given for 12 days to one person and twice for 16 days to the other. Resin administration was accompanied by acidosis. The total potassium deficit amounted to about 700, 500, and 800 m.eq. in the three experiments.

The urine-potassium level fell below the plasma-potassium level, showing that the kidney tubules can reabsorb potassium against a concentration gradient. Reabsorption was maximal during the recovery period, after the acidosis had been corrected.

If patients with potassium deficiency continue to lose potassium, it may be because of disturbances in acid-base balance or because of adrenal overactivity, but not because of any inherent property of the kidney to waste potassium.

I am indebted to Prof. L. J. Witts, in whose department this work was done; to Mr. G. Higgins, of the department of clinical biochemistry of the University of Oxford, for the serum analyses; to Miss Alison Shepherd and Miss Barbara Seibert for technical assistance; to Miss M. C. McLarty for help with the figures; and to the Medical Research Council for a grant for expenses.

REFERENCES

Albright, F., Reifenstein, E. C. jun. (1948) The Parathyroid Glands and Metabolic Bone Disease. Baltimore.
Atchley, D. W., Loeb, R. F., Richards, D. W. jun., Benedict, E. M., Driscoll, M. E. (1933) *J. clin. Invest.* 12, 297.
Berliner, R. W., Kennedy, T. J. jun., Orloff, J. (1951) *Amer. J. Med.* 11, 274.
Black, D. A. K. (1951) Personal communication.
Danowski, T. S. (1949) *Amer. J. Med.* 7, 525.

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DR. FOURMAN: REFERENCES—*continued*

Darrow, D. C., Pratt, E. L. (1950) *J. Amer. med. Ass.* 143, 365, 432.
Eliel, L. P., Pearson, O. H., Rawson, R. W. (1950) *New Engl. J. Med.* 243, 471, 518.
Fourman, P., Bartter, F. C., Albright, F., Dempsey, E., Carroll, E., Alexander, J. (1950) *J. clin. Invest.* 29, 1462.
Hald, P. M. (1951) *In* Visscher, M. B., Methods in Medical Research. Chicago; vol. IV, p. 79.
Mateer, F., Greenman, L., Peters, J. H., Gow, R. C., Danowski, T. S. (1949) *Fed. Proc.* 8, 107.
Tarail, R., Elkinton, J. R. (1949) *J. clin. Invest.* 28, 99.

EFFECT OF 3 : 5 : 3′-L-TRIIODOTHYRONINE IN MYXŒDEMA

J. GROSS
M.D., Ph.D. McGill
MERCK FELLOW IN NATURAL SCIENCES, NATIONAL RESEARCH COUNCIL OF CANADA

ROSALIND PITT-RIVERS
M.Sc., Ph.D. Lond.
From the National Institute for Medical Research, Mill Hill, London

W. R. TROTTER *
D.M. Oxfd, M.R.C.P.
From the Medical Unit, University College Hospital Medical School, London

3 : 5 : 3′-L-triiodothyronine has been shown to be a normal constituent of human plasma (Gross and Pitt-Rivers 1951, 1952a) and to possess several times the activity of L-thyroxine in the prevention of goitre in rats (Gross and Pitt-Rivers 1952b).

We report here data which indicate that triiodothyronine was highly effective in causing a return of both gaseous and cholesterol metabolism to normal levels in two cases of hypothyroidism.

L-triiodothyronine was dissolved in 0·0004 *N* sodium hydroxide and autoclaved for 30 minutes at a pressure of 10 lb.; the autoclaved solution was analysed by paper chromatography at the beginning and end of the course of treatment; neither thyroxine nor any organic iodine-containing compound other than triiodothyronine was detected.

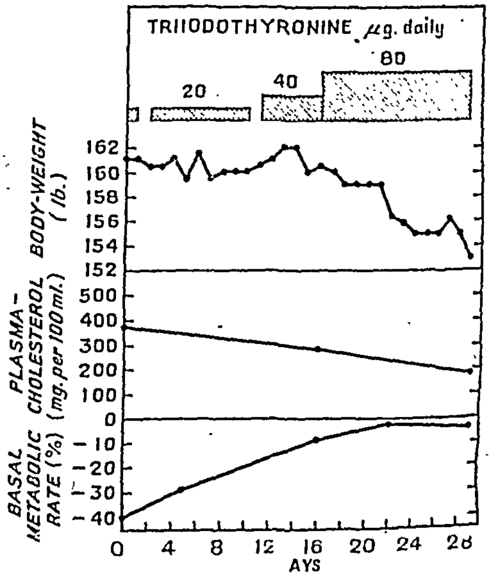

Fig. 1—Action of 3 : 5 : 3′-L-triiodothyronine in case 1.

The metabolic findings are summarised in figs. 1 and 2.

CASE-RECORDS

Case 1.—A married woman, aged 75, had for the past two years had breathlessness with precordial pain, and attacks of giddiness with unsteady gait. She felt the cold severely, she had become progressively more deaf, and her hair was falling out. For the last two years her skin had been dry and flaky.

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* In receipt of a grant from the Sir Halley Stewart Trust.

On examination she had a typical myxœdematous appearance: her face was puffy, she had a pronounced malar flush, her eyebrows and hair were scanty, and her skin was harsh, dry, and desquamating. She spoke slowly in a hoarse low-pitched voice. Mentally she was alert and well orientated. Her basal metabolic rate (B.M.R.) was −40% and plasma-cholesterol level 390 mg. per 100 ml. Measurement of the radio-iodide concentration by the method of Stanley and Astwood (1948) showed that there was no functioning thyroid tissue.

Treatment was begun with a single dose of intramuscular L-triiodothyronine 20 µg., and after a day's interval this dose was given daily for nine days. The dose was then increased to 40 µg. daily for a further five days, and thereafter to 80 µg.

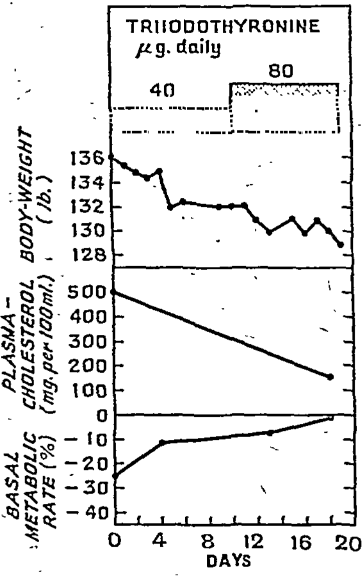

Fig. 2—Action of 3 : 5 : 3′-L-triiodothyronine in case 2.

Progress.—After a total course of twenty-nine days the patient's condition had manifestly improved. Her face was less puffy and she felt more energetic and cheerful. Her voice was now normal. The B.M.R. had risen to −4%, the plasma cholesterol level had fallen to 170 mg. per 100 ml., and she had lost 9 lb. in weight. She left hospital on an oral maintenance dose of sodium L-thyroxine.

Case 2.—A housewife, aged 58, complained of tiredness and breathlessness for the last three or four years, and of generalised aches and pains, and numbness of the extremities. She disliked cold weather. There had been no loss of hair.

On examination she was garrulous and her voice was somewhat husky. There was a little puffiness of the face and fingers. The skin was dry. The initial B.M.R. was −25%, and the plasma-cholesterol level 510 mg. per 100 ml. Radio-iodide concentration, measured by the method of Stanley and Astwood (1948), indicated that thyroid function was much less than normal.

Treatment was begun with intramuscular L-triiodothyronine 40 µg. daily, increased later to 80 µg.

Progress.—After nine days' treatment the patient noticed that she was less breathless, and by the nineteenth day, when the drug was discontinued, she felt much more energetic and cheerful. She was noticeably brighter, and her face was no longer puffy. By this time she had lost 7 lb. in weight, the B.M.R. was −1%, and the plasma-cholesterol was 150 mg. per 100 ml. Treatment was continued with sodium L-thyroxine orally.

DISCUSSION

Gross and Pitt-Rivers (1952b) have shown that L-triiodothyronine has a thyroid-hormone-like action on the hypophysis. From the present results it is clear that its peripheral effects also resemble those of the thyroid hormone. There is not yet sufficient clinical evidence for quantitative comparison with thyroxine; nevertheless a dose of 80 µg. of L-triiodothyronine daily seems to be within the range of normal requirement in man and to have an effect similar to that of a daily oral dose of 100–300 µg. of L-thyroxine. L-triiodothyronine is therefore at least as active on peripheral metabolism as is L-thyroxine. Further experiments are now being made to determine the relative activities of the two compounds.

These results, and the fact that triiodothyronine is present in normal plasma, suggest that it may be the compound directly responsible for the peripheral action of the thyroid gland.

It is not suggested that this compound is likely to take the place of either thyroid extract or thyroxine in clinical use.

SUMMARY

3 : 5 : 3′-L-triiodothyronine has been administered to two hypothyroid patients in a maximal daily dose of 80 µg. The B.M.R. and blood-cholesterol levels returned to normal on this dosage; at the same time the patients lost weight during the treatment.

Our thanks are due to Dr. Kenneth Harris for permission to treat case 2.

REFERENCES

Gross, J., Pitt-Rivers, R. (1951) *Lancet*, ii, 766.
— — (1952a) *Ibid*, i, 439.
— — (1952b) *Ibid*, p. 593.
Stanley, M. M., Astwood, E. B. (1948) *Endocrinology*, 42, 107.

CONTROLLED HYPOTENSION AND ITS EFFECT ON RENAL FUNCTION

BARBARA EVANS
M.R.C.S.
PATHOLOGIST, QUEEN VICTORIA HOSPITAL, EAST GRINSTEAD

G. E. HALE ENDERBY
M.A., M.B. Camb., D.A.
ANÆSTHETIST, QUEEN VICTORIA HOSPITAL, ROYAL NATIONAL ORTHOPÆDIC HOSPITAL, AND METROPOLITAN EAR, NOSE, AND THROAT HOSPITAL

IN order to investigate the renal effects of hypotension and postural ischæmia induced with hexamethonium bromide in surgical operations (Enderby 1950, Enderby and Pelmore 1951) investigations were first made on 50 patients who did not receive hexamethonium during their operations.

These control cases were taken consecutively, without particular reference to the type of operation, but excluding any who showed preoperative proteinuria or were known to have renal abnormality. Induction of anæsthesia was with thiopentone assisted by a muscle relaxant, and maintenance by nitrous oxide and oxygen (2 : 1) in semi-closed circle absorber with intermittent doses of thiopentone delivered through a Gordh needle. The blood-pressure followed a normal anæsthetic course: exact figures were not obtained but undue hypotension was not observed. The operations were mainly plastic, and almost all the patients had had one or more previous operations. They were drawn from a reasonably healthy cross-section of the community.

The urine was examined preoperatively and for three to seven days after operation. The boiling and acetic acid test was used for protein; blood-urea was estimated by the urease-nesslerisation method of Archer and Robb; and the urinary deposit was examined microscopically.

A similar group of patients receiving hexamethonium bromide during operation was investigated simultaneously in the same manner. Again excluding those with proteinuria or renal abnormality before operation, 50 cases were studied. During operation their systolic blood-pressure fell to levels between 55 and 80 mm. Hg, as measured by oscillation of a mercury column with the cuff on the patient's arm. The technique of anæsthesia was the same as that used in the controls.

RESULTS

In the accompanying table the controls and the experimental series are compared as regards incidence of proteinuria, persistence of proteinuria for more than three days, and presence of red corpuscles and casts in the urine. Although it appeared during the investigation that the hexamethonium cases were showing casts and

URINARY ABNORMALITIES OBSERVED AFTER ANÆSTHESIA IN 50 CONTROLS NOT GIVEN HEXAMETHONIUM BROMIDE AND 50 PATIENTS GIVEN THE DRUG

Abnormality	Controls	Given hexa-methonium	Difference (%)	S.E. of difference	Significance
Proteinuria on one or more of 3 postoperative days	39 (78%)	46 (92%)	14	7·02	Not significant
Proteinuria persisting for more than 3 days	17 (34%)	27 (54%)	20	9·7	Doubtful
Red cells and casts present on one or more of 3 post-operative days	2 (4%)	7 (14%)	10	5·6	Not significant
Red cells and casts persisting for more than 3 days	0	2 (4%)	4	..	..

red cells in excess of the controls there is no statistically significant difference between the two groups.

Two patients, each treated with and without hexamethonium during consecutive and similar operations, were investigated in greater detail especially as regards fluid intake and output for five days postoperatively.

Case 1.—A woman, aged 25, had no proteinuria before operation but had persistent proteinuria for five consecutive postoperative days. The anæsthetic used was thiopentone 1·25 g., 'Flaxedil' 80 mg., and gas-and-oxygen. No hexamethonium bromide was given. The blood-pressure ran a normal anæsthetic course, and undue hypotension was not observed. The blood-urea level was 37 mg. per 100 ml. the morning after the operation. Fluid intake was 236 oz. and the output 200 oz. over the next six days.

At her next operation three months later she was given hexamethonium bromide 100 mg., but the other conditions were as nearly as possible identical. Her blood-pressure ran at 60–80 mm. Hg for one and a half hours. Proteinuria was present for five consecutive postoperative days and the blood-urea level on the fourth postoperative day was again 37 mg. per 100 ml. The fluid intake over these six days was 275 oz. and the output 218 oz.

Case 2.—A woman, aged 57, was operated on without hexamethonium bromide, when the blood-pressure ran a normal anæsthetic course for one and three-quarter hours. Proteinuria persisted for eight days. The intake was 496 oz., and the output 361 oz. over five days, the blood-urea level being then 36 mg. per 100 ml.

Three months later a similar plastic operation was performed. The anæsthetic was the same (thiopentone 1 g., flaxedil 80 mg.) but hexamethonium 50 mg. was also given. The blood-pressure ran at 50–85 mm. Hg for one and three-quarter hours. Proteinuria was still present on the thirteenth day on the patient's discharge. The blood-urea level was then 38 mg. per 100 ml., the fluid intake 217 oz., and output 183 oz. (five days).

The proteinuria in these two cases was no more than a trace, and the urinary output was satisfactory on each occasion.

DISCUSSION

Comparison of our two series suggests, therefore, that in previously healthy people the hypotension induced with hexamethonium for surgical purposes has little effect on renal function. This fits in with the recent work of Miles et al. (1952), who showed that after the administration of pentamethonium bromide during anæsthesia the blood-pressure dropped to 50–70 mm. Hg, yet the renal blood-flow remained almost unchanged. We should make it clear, however, that our conclusion applies only to the *normal* kidney.

SUMMARY

50 patients receiving hexamethonium bromide during anæsthesia were compared with 50 not receiving the drug, special reference being made to proteinuria and fluid excretion.

Although proteinuria with or without casts and red cells was commoner in the hexamethonium series, the difference is of doubtful or negative statistical significance.

The conclusion may be drawn that if renal function is normal before operation, it is unlikely to be appreciably impaired by hypotension induced for surgical purposes with hexamethonium bromide.

Our thanks are due to the surgeons of the Queen Victoria Hospital, East Grinstead, for the use of their cases.

REFERENCES

Enderby, G. E. H. (1950) *Lancet*, i, 1145.
— Pelmore, J. F. (1951) *Ibid*, i, 663.
Miles, B. E., de Wardener, H. E., Churchill-Davidson, H. C., Wylie, W. D. (1952) *Clin. Sci.* 11, 73.

IRRADIATION OF RETINOBLASTOMA

(GLIOMA RETINÆ)

H. B. STALLARD
M.B.E., M.A., M.D. Camb., LL.D., F.R.C.S.
SURGEON, MOORFIELDS EYE HOSPITAL; OPHTHALMIC SURGEON, ST. BARTHOLOMEW'S HOSPITAL, LONDON

Ellinger (1941) has stated that "tumours arising in radio-resistant tissue are invariably radio-refractory and are to be described as radio-resistant tumours." This is not true of retinoblastoma (glioma retinæ); for, although the retina, in common with other parts of the nervous system, is resistant to irradiation, even in doses which are several times more than that which injures blood-forming tissues, the undifferentiated atypical cells of retinoblastoma are highly radiosensitive. So in the case of this neoplasm there is the unique and favourable condition of a very radiosensitive growth arising from relatively radioresistant tissue. These facts are proved clinically by the results of properly applied irradiation and are verified by the histological examination of serial sections of eyes irradiated for retinoblastoma.

DIAGNOSIS

The tragedy of retinoblastoma is that in a high proportion of cases (about 40%) both eyes are affected, and that it is often missed in infant clinics and child-welfare centres, no heed being taken of the mother's observation about the "cat's-eye" reflex. By the time this greyish-white fundus reflex is evident, the neoplasm is large enough to be obvious either on focal illumination through the dilated pupil with a fine pencil of light shone obliquely into the eye in a dark room, or by ophthalmoscopy. The neoplasm is white, with a flocculent granular surface, and there are loops of thin-walled blood-vessels (fig. 1). It is generally hemispherical, and it may project either into the vitreous or between the retina and choroid (causing a retinal detachment) or may extend both ways.

When both eyes are affected, the growth is more advanced in one eye than in the other. The detection of islands about 1 mm. in diameter at or near the ora serrata requires expert ophthalmoscopy. When the macula is involved, a squint may be present, and the child may be brought because of this.

In a neglected case the intra-ocular pressure rises above physiological limits (hydrophthalmia, infantile glaucoma), the ocular tunics become stretched, and the eye is enlarged. Ultimately the neoplasm bursts through the corneoscleral junction, fills the orbit, infiltrates the walls thereof and projects as a soft bleeding fungating mass on the child's face.

PROGNOSIS

Retinoblastoma is a highly malignant neoplasm, and multiple islands may be present at the same time in the retina or develop subsequently in other parts of the membrane. The optic nerve, and (more rarely) the orbital tissues become infiltrated, retinoblastoma extends intracranially, and metastases occur in other parts of the body. Parts of the optic nerve may show deposits of neoplastic cells, the intervening portion remaining free from the growth.

The prospect of successful irradiation is good when the retinoblastoma affects a third or less of the retina and has not invaded the optic disc. It is, however, most unlikely that even "guiding vision" will be saved when more than half the retina has been destroyed by the neoplasm. In such advanced cases, even when the retinoblastoma is completely destroyed, complications such as complete retinal detachment, severe intra-ocular hæmorrhage, iridocyclitis, and endophthalmitis render the eye blind.

It is therefore essential to diagnose the neoplasm as soon as possible and to make follow-up ophthalmoscopic examinations, with the pupil fully dilated, at monthly intervals until the child is 5 years of age, for islands of the neoplasm may develop near the ora serrata, or indeed anywhere in the retina; and when they are small—and therefore favourable for treatment—they may be overlooked.

PATHOLOGY

Fig. 2 shows the ophthalmoscopic appearance of a successfully irradiated area of retinoblastoma. At the site of the neoplasm is a dense white scar surrounded by a crenated fringe of pigment. The retinal vessels in this area are attenuated, some are totally occluded, and white perivascular sheathing is present in others. The adjacent retina and choroid are atrophic, pale, and stippled with fine irregular dots of pigment.

A study of serial sections through such a degenerate disorganised atrophic area showed a considerable reduction in the vascularity of the choroid and retina. A few vessels were varicose and distended with blood, others were collapsed and invisible, and in some only the naked elastic membrane remained without endothelium to line the lumen. The collagen fibres of the tunica adventitia had become fewer and thicker. Some had merged together; others were separated, had become wavy, and projected into the surrounding tissues at angles, ultimately becoming granular and disappearing. Four or five months after irradiation there was no adventitia. The muscle-fibres of the tunica media became swollen, the nuclei enlarged, and some of the cells degenerated. In this atrophic and disorganised area of retina there were very few retinoblastoma cells. Such as were present were irregular clumps of distorted inactive cells compressed by fibrous tissue. In one instance islands of retinoblastoma cells, with the nucleus staining well and histologically not necrotic, remained apparently inactive until the child died from recurrences in the orbit of the excised eye nearly a year after irradiation of the remaining eye. In one published case clumps of retinoblastoma cells remained thus for eight years without proliferation.

Other changes were fibrosis, œdema, cystic spaces, deposits of pigment, irregular areas of homogeneous exudate and hyaline material, calcification, and retinal hæmorrhages.

The destruction by irradiation of a large mass of retinoblastoma occupying more than half the eye may produce a toxin which ultimately causes endophthalmitis. Iridocyclitis and complicated glaucoma were sequels which were rarer after treatment by radon seeds and radium discs than after deep X-ray therapy.

COMPARATIVE THERAPEUTIC VALUES OF RADIUM AND DEEP X RAYS

Should retinoblastoma be treated by radium or by deep X rays? The statistics shown in fig. 3 are taken from the results in:

(1) A series of 29 unselected cases, 16 of which I treated with 2 mC radon seeds in 1934–48, and 13 (14 eyes) with curved radium discs in 1948–51.

(2) A series of 5 patients treated with radon seeds in 1929–37 by Foster Moore.

(3) 17 patients treated by other surgeons in Great Britain, Canada, Australia, and the U.S.A.

(4) 8 cases treated with radium needles at the Christie Hospital and Holt Radium Institute, Manchester, in 1935–49.

Radium Therapy

In my series of 29 patients (30 eyes) (see fig. 3) treated with radon seeds and radium discs 24 (83%) have some useful vision and have so far shown no evidence of recurrence in the irradiated eye. Of these, 7 are alive more than five years after irradiation—i.e., after periods of seventeen, sixteen, fifteen, fourteen, thirteen (2 cases), and five years. The vision is 6/6 in 10 cases, so far as can be judged by illiterate tests; 6/9 (6/6 partly) in 1

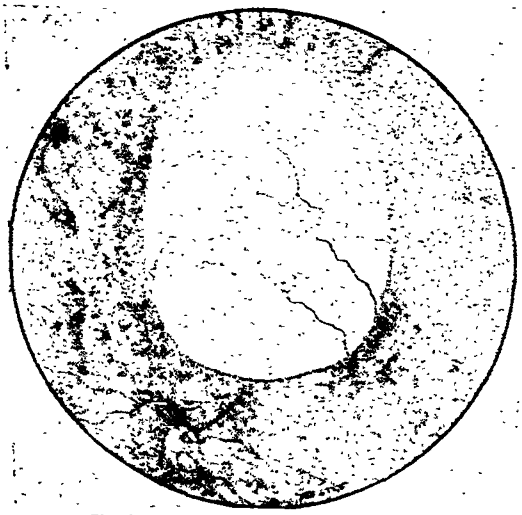

Fig. 1—Retinoblastoma before irradiation.

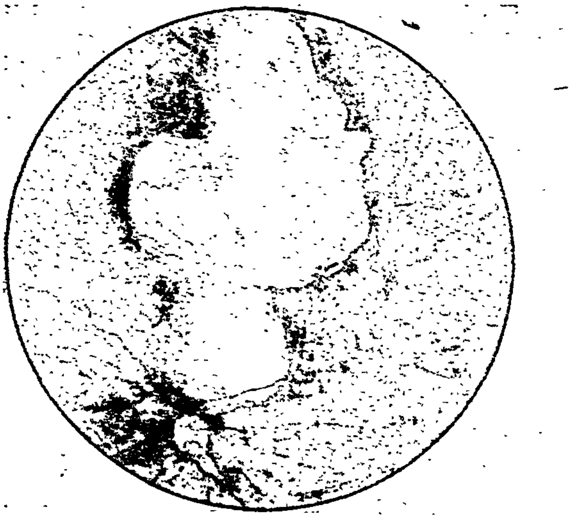

Fig. 2—Same retinoblastoma as in fig. 1 after irradiation.

case; 6/24 in 1 case where the macula was involved in the growth, and in 1 case of aphakia and perimacular exudates; 6/36 in 1 case, and 6/60 in 2 cases of macular involvement; and perception of light in 1 case. The 7 remaining patients (1 with two irradiated eyes) are still too young for any reasonable estimate of their vision. It has been remarkable that 4 patients with the scar of the successfully irradiated neoplasm obliterating the papillomacular region have been able to use the nasal part of their retina to read. One boy reads Jaeger 4 and draws very accurately. Of the 5 (17%) failures, 2 are blind, but have kept their remaining irradiated eye, and have shown no sign of recurrence, one for fourteen years and the other for twelve years since the application of radon seeds. In 3 cases the irradiated eye was excised—because of total retinal detachment in 2 cases and vitreous hæmorrhage and complicated glaucoma in the third. Serial sections of these eyes showed no clear histological evidence of active retinoblastoma cells.

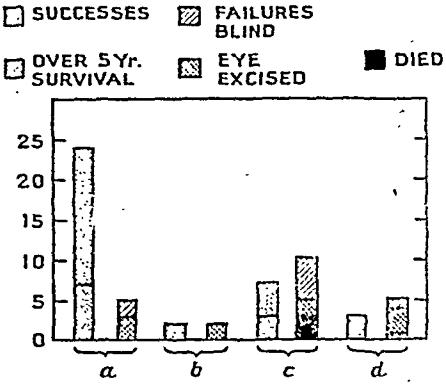

Fig. 3—Results in four series treated with radon and radium.

a, My own series of 29 cases; 16 treated with radon seeds (1934–48) and 13 (14 eyes) treated with radium discs (1948–51).

b, Mr. Foster Moore's series of 4 patients (1 who died of intercurrent disease soon after operation has been excluded) treated with radon seeds (1929–37).

c, 17 patients treated by other surgeons.

d, 8 patients treated with radium needles at Christie Hospital and Holt Radium Institute (1935–49).

Of Foster Moore's 5 patients (fig. 3) 4 have survived, 2 with sufficient vision to enable them to earn a living; 2 are blind, one from endophthalmitis and the other from severe intra-ocular hæmorrhage, iridocyclitis, and complicated glaucoma, which developed eleven months after successful irradiation. The remaining patient died of gastro-enteritis during postoperative convalescence.

Among the 17 patients treated by other surgeons (fig. 3) there were 7 successes, 3 alive five years after treatment. The 10 failures illustrate in my view the damaging effect of certain radium techniques.

4 of them were treated by means of a Columbia-paste -plaque, with radium needles applied externally over the orbit. 2 of these were blinded by dense vascularised opacification of the cornea, and 2 died from metastases. 2 patients, who had radium needles inserted round the eye, each lost their irradiated eye from complicated glaucoma.

In all these 6 cases the islands of retinoblastoma were small, and, according to my experience, should have responded to treatment with either a radon seed or a radium disc fixed to the sclera at the appropriate site.

Of the remaining 4 failures 1 died of metastases, 2 became blind from total retinal detachment, and 1 had too much irradiation for the eye to retain any useful function.

At the Christie Hospital and Holt Radium Institute, Manchester, in 1935–49 (fig. 3) the remaining eye of 6 patients and both eyes of 2 patients were treated by the insertion of radium needles through the skin of the eyelids posteriorly into the orbit, where their points converged to make a truncated cone. The active length of the needles varied from 1·5 to 4·5 cm. In some cases four needles were also disposed as a coronal frame in the orbit about the plane of the equator of the eyeball. The distribution of the needles was made regardless of the site of the retinoblastoma, which in 4 instances occupied less than one quadrant of the eye and in another case was at the papillomacular area and measured 6 × 4·5. mm. Of the 8 children thus treated, 3 have some vision. Of the 5 failures 1 is blind in both eyes, which he has retained; 3 have had their blinded eyes removed; and 1 died after an orbital recurrence.

Deep X-ray Therapy

Reese (1951) rightly remarks that there are appreciable technical difficulties in firing accurately a narrow pencil of X rays on to the retina of a conscious infant with avoidance of the anterior segment of the eye for as many as 28 treatments of seven to eight minutes' duration twice a week for three and a half months. If the beam deviates by 1 or 2 mm. the anterior segment will be irradiated and cataract, iridocyclitis, and atrophy of the globe may follow. In 8 of 53 patients exposed (in 1934–49) to the transnasal field of fire, development of the nasal bridge was arrested, causing saddle-shaped deformity (Reese 1951), and irradiation sarcoma developed in the temporalis muscle and bones of the face in 4 patients seven or more years after treatment. Intra-ocular hæmorrhages occurred in 18, glaucoma in 9, and in 18 the irradiated eye became atrophic and shrank (fig. 4). The results in Reese's series of 53 patients were: visual acuity 20/200 or better 25, blind 16, and died 12.

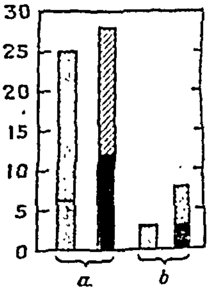

Fig. 4—Results in two series treated with deep X rays.

a, Dr. A. B. Reese's series of 53 patients (1934–49).

b, Prof. B. W. Windeyer's series of 11 patients (1941–47).

Of a series of 11 children treated with deep X rays by Prof. B. W. Windeyer in 1941–47 (fig. 4) 3 were living with some vision in the irradiated eye five years after treatment, 3 had died of the disease, and 5, though still alive, had had the irradiated eye excised because of failure to arrest the neoplasm. 4 developed irradiation cataract, and retinal detachment occurred in 3.

CONCLUSION

Study of these series has convinced me that, when a third or less of the retina is involved in a retinoblastoma, there is reasonable hope that the new growth may be destroyed by irradiation. With very few exceptions the results are bad when half or more of the retina is already destroyed. In such cases retinal detachment is generally present, and if it is not it will almost certainly occur after irradiation. Later sequels are severe intra-ocular hæmorrhage, iridocyclitis, complicated glaucoma, and endophthalmitis. Irradiation often fails when the choroid is infiltrated. So it seems advisable in such advanced cases to excise the eye with 10 mm. of the optic nerve and to give postoperative irradiation of the orbit. In no instance in this series was irradiation of the eye of such patients worth while.

The dose is still empirical. It is a fact that the neoplasm in some patients is more radiosensitive than in others, and I think it is evident that the retinoblastoma is more radiosensitive than the more highly differentiated neuro-epithelioma. It seems that a dose of 2500–3000 r at the summit of the neoplasm and up to 6000–8000 r at its base is generally effective.

In my opinion it is desirable to bring the therapeutic artillery as close as possible to the target and to hit it hard and quickly with a concentration of fire that is known to be both effective and reasonably safe for the eye. To achieve this I think that radium discs, made to fit the scleral curvature evenly, are better than radon seeds and other applicators used hitherto. This technique is preferable to long-range shooting with heavy doses from radium needles fixed in Columbia-paste plaques or from the radium bomb, for both of these methods are disastrous for the eye and quite often fail to destroy the neoplasm completely.

Although deep X-ray treatment is successful in some cases, where less than a third of the retina is affected by the neoplasm, it has the technical disadvantage of protracted treatment—the difficulty of maintaining the necessary immobility of a child's head during treatment—and it produces a higher incidence of serious complications than is seen after the application of a radium disc or a radon seed. Fig. 3 shows that in several series in which the size of the retinoblastoma was fairly comparable the results of treatment with radon seeds and radium discs were appreciably better than the results of treatment with deep X rays (fig. 4), radium plaques applied externally, or radium needles inserted into the orbital tissues round the eye.

I am very grateful to Professor Windeyer, of the Middlesex Hospital, and to Dr. Ralston Paterson, Dr. J. L. Dobbie and Dr. Margaret Tod, of the Christie Hospital and Holt Radium Institute, for their kindness in affording me facilities to examine their case-records and pathological material and for their helpful advice. I thank Dr. Algernon B. Reese for his good counsels in private communications and for the mass of interesting information to be obtained from his papers on the treatment of retinoblastoma with deep X rays. I am much in the debt of my old chief, Mr. Foster Moore, with whom I was privileged to be associated in his pioneer work of treating retinoblastoma with radon seeds. Lastly, I thank a number of colleagues who have been kind enough to send me their patients for radiotherapy.

BIBLIOGRAPHY

Ballantyne, A. J. (1941) *Proc. R. Soc. Med.* 35, 345.
— Michaelson, I. C., Heggie, J. F. (1938) *Trans. ophthal. Soc. U.K.* 58, 255.
Bloom, W. (1948) Histopathology of Irradiation from External and Internal Sources. New York and London.
Desjardins, A. U. (1931) *Amer. J. Roentgenol.* 26, 639.
Ellinger, F. (1941) The Biologic Fundamentals of Radiation Therapy. New York.
Flexner, S. (1891) *Johns Hopk. Hosp. Bull.* 2, 115.
Gibson, W. L. (1947) *Trans. ophthal. Soc. Aust.* 7, 77.
Glücksmann, A., Tansley, K. (1936) *Brit. J. Ophthal.* 20, 497.
— Wilson, C. W. (1945) *Brit. J. Radiol.* 18, 158.
Goldstein, I., Wexler, D. (1931) *Arch. Ophthal.* 5, 591.
Greeves, R. A. (1934) *Trans. ophthal. Soc. U.K.* 54, 420.
Griffith, A. (1933) *Ibid*, 53, 238.
Japha, E. M. (1949) *Brit. J. Cancer*, 3, 16.
Johnston, K. B. (1949) *Trans. Canad. ophthal. Soc.* 12, 34.
Joyce, A. (1944) *Trans. ophthal. Soc. Aust.* 4, 98.
King, E. F. (1948) *Proc. R. Soc. Med.* 41, 268.
Laval, J. (1950) *Arch. Ophthal., Chicago*, 44, 140.
Law, F. W. (1948) *Trans. ophthal. Soc. U.K.* 68, 377.
MacCallan, A. F., Cade, S., King, E. F. (1934) *Ibid*, 54, 201.
McDowall, V., Marks, E. O. (1932) *Brit. J. Ophthal.* 16, 686.
Martin, H. E., Reese, A. B. (1940) *Trans. Amer. Acad. Ophthal. Oto-laryng.* 45, 70.
— — (1942) *Arch. Ophthal., Chicago*, 27, 40.
— — (1945) *Ibid*, 33, 429.
Martin, P. (1933) *Trans. ophthal. Soc. U.K.* 53, 246.
Meighan, S., Michaelson, I. C. (1938). *Ibid*, 58, 208.
Moore, R. F. (1929) *Proc. R. Soc. Med.* 22, 951.
— (1933) *Ibid*, 26, 1036.
— (1933) *Trans. ophthal. Soc. U.K.* 53, 215.
— (1935) *Ibid*, 55, 3.
— Stallard, H. B., Milner, J. G. (1931) *Brit. J. Ophthal.* 15, 673.
Philps, S. (1944) *Trans. ophthal. Soc. U.K.* 64, 107.
— Houlton, A. C. L. (1944) *St. Bart's. Hosp. J.* 47, 278.
Ray, B. S., McLean, J. M. (1943) *Arch. Ophthal., Chicago*, 30, 437.
Reese, A. B. (1951) Tumours of the Eye. London.
— Merriam, G. R. jun., Martin, H. E. (1949) *Amer. J. Ophthal.* 32, 175.
Snell, A. C. (1936) *Trans. ophthal. Soc. U.K.* 56, 269.
Spear, F. G. (1935) *Brit. J. Radiol.* 8, 68, 280.
Stallard, H. B. (1932) *Brit. J. Ophthal.* suppl. no. 6.
— (1933) *Trans. ophthal. Soc. U.K.* 53, 224.
— (1936) *Proc. R. Soc. Med.* 29, 963.
— (1936) *Brit. med. J.* ii, 962.
— (1938) *Brit. J. Ophthal.* 22, 604.
— (1948) *Ibid*, 32, 618.
Tansley, K. (1933) *Ibid*, 17, 321.
— Spear, F. G., Glücksmann, A. (1937) *Ibid*, 21, 273.
Tribondeau, L., Belley, G. (1907) *Arch. Elec. méd.* 15, 907.
— — (1907) *C.R. Soc. Biol. Paris*, 63, 128.
Waldman, J. (1940) *Arch. Ophthal., Chicago*, 23, 55.
— Shannon, C. E. G. (1949) *Ibid*, 41, 32.

Preliminary Communication

A VARIANT OF COWPOX VIRUS

MANY of the earlier studies on variation among bacteria have been facilitated by the atypical appearance of the colony form of the variant on solid media. Variation in the form or size of the bacteriophage plaques produced by bacteriophage growing on susceptible bacteria on solid media has been similarly used, but generally animal virus mutants cannot be detected readily by such simple means.

The appearances of the lesions produced by viruses which infect the chorio-allantois of chick embryos provides the nearest approach to the application of similar methods in the study of viruses. The virus lesion in this case, however, is the visible manifestation of tissue reaction to local growth of virus; but the method has had little application in the detection of virus variants. Because of the characteristic lesions produced on the chorio-allantois the viruses of the pox group seem to be especially suitable for this method of study. We report here the occurrence in cowpox strains of a variant which produces atypical lesions on the chorio-allantois.

TYPICAL LESION

The virus responsible for the natural pox of cattle produces typically hæmorrhagic lesions on the chorio-allantoic membrane.[1] Three days after inoculation of a suitable dose of virus the discrete lesions are about as large as those produced by vaccinia virus—i.e., about 2 or 3 mm. in diameter—but they vary in colour from bright pink to deep red owing to hæmorrhage from vessels in the inflamed and thickened ectoderm and in the immediately subjacent mesoderm. All nine strains of virus which we have isolated from lesions in cattle or persons infected from them have regularly produced hæmorrhagic lesions on egg membranes and in the skin of rabbits and guineapigs.

WHITE LESIONS

In the course of repeated passage of strains during the last few years, however, conspicuous white lesions have occasionally appeared among the typical deep red "colonies" on the membrane. Of the last six strains, isolated in 1947–49, two showed on primary isolation by chorio-allantoic inoculation white lesions in an otherwise hæmorrhagic take. A large inoculum of passage virus produces a completely hæmorrhagic confluent take, and in such membranes the white variant may not be apparent. When the inoculum is adjusted to obtain discrete lesions on the chorio-allantois, single white lesions have often appeared among the red ones. The proportion of white to red lesions has varied but, in strains passed routinely with a suitably diluted inoculum, has never been more than 1 to 40. The high incidence of the variant indicates a high degree of instability of our cowpox strains in chick embryos.

ISOLATION OF WHITE VARIANT

By cutting out a white lesion well separated from the usual red lesions and inoculating further membranes from it the proportion of variant lesions can be increased until after several such passages a virus producing only white lesions has been obtained. Aspirating a white lesion with a fine capillary pipette and using the aspirated material diluted in broth for further inoculation facilitates the isolation of a virus which no longer produces hæmorrhagic lesions on the chorio-allantois.

In this way we have isolated, from the three strains with which the attempt has been made, non-hæmorrhagic variants which have bred true. One of these obtained from a strain first isolated in 1938 has so far been subcultured on the chorio-allantois 17 times without showing any signs of reversion to its original property of producing hæmorrhagic lesions on the chorio-allantois. On the other hand, repeated selection and subculture of single red colonies in the same way still produces infection on the chorio-allantois in which occasional white variants appear. The permanence of the distinguishing characteristics of the white variant suggests that it represents a mutation occurring with an unusually high frequency.

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[1] Downie, A. W. *J. Path. Bact.* 1939, 48, 361.

CHARACTERS OF WHITE VARIANT

Apart from the loss of the ability to induce hæmorrhage the histological appearances of the white lesions show other differences from those usually produced by cowpox strains. These differences will be described elsewhere.

The white variant also differs from the parent strain in the character of the "take" on the skin of rabbits infected by scarification or by intradermal inoculation. Here also the hæmorrhagic appearance characteristic of the original virus strains is absent. The lesions produced in the rabbit skin by the white variant are very similar in appearance to the lesions produced by strains of vaccinia virus.

Serological studies to be described elsewhere have not yet elicited any immunological differences between the white variants and the original cowpox strains.

Dr. F. Dekking, of Amsterdam, working with one of our strains and with strains isolated by him in Holland, has confirmed many of our observations (personal communication, 1951).

COMMENT

When the white variant was first encountered, we naturally considered the possibility of contamination of our cowpox strains with a vaccinia virus or possibly with some micro-organism such as those of the pleuro-pneumonia group. We believe that we have excluded such possibilities. As noted above, the white variant in many respects closely resembles vaccinia virus, and its occurrence obviously bears on the disputed question whether current vaccinia-virus strains, which in the laboratory usually produce lesions lacking the hæmorrhagic character of cowpox infections, may have been derived by loss variation from cowpox strains. The white cowpox variant differs in certain other properties from the strains of vaccinia available to us; but it seems possible that repeated propagation of a white cowpox variant may have eventually given rise to strains of vaccinia virus in use at present.

Repeated subculture of cowpox strains on the chorio-allantois, large inocula being used in routine transfers, does not lead to replacement of the usual virus by the white variant. Indeed we have evidence that in this tissue white variants mixed with the parent strain rapidly become overgrown by it.

Nor has repeated propagation of cowpox virus in the skin of rabbits over many years led to the emergence of the white variant. We have, however, no knowledge of the survival value of the white variant on repeated artificial propagation of cowpox virus on the skin of calves or sheep in the preparation of vaccine lymph or in the human skin on arm-to-arm vaccination which was practised during last century. Such conditions may have provided an opportunity for the appearance of vaccinia strains as we know them today from a cowpox variant such as that described here.

A. W. DOWNIE
M.D., D.Sc. Aberd.
D. W. HADDOCK
M.B. Lpool

Department of Bacteriology,
University of Liverpool

Medical Societies

ROYAL SOCIETY OF MEDICINE

Agents in Milling and Baking

THE section of experimental medicine and therapeutics of the Royal Society of Medicine met on May 13, under the chairmanship of Prof. R. A. MCCANCE, F.R.S., the section's president, to discuss certain agents used in milling and baking.

Mr. J. B. M. COPPOCK, PH.D., outlined the factors which determine bread quality, including the type of wheat, extraction of flour, and the age of the flour. When flour is stored its baking qualities and colour improve, but economically it is not feasible to store flour for the time necessary (some months) for optimum improvement. Certain chemicals can bring about this improvement without storage. Some of these—e.g., potassium bromate, ammonium persulphate, and ascorbic acid—affect only the texture of the bread. Others—e.g., nitrogen trichloride (agene) and chlorine dioxide—not only improve the crumb texture but also bleach or whiten the bread. With a sufficiently long fermentation-time the baker could produce satisfactory bread from untreated flour, but this is also ruled out on labour and other grounds; in fact the baker himself may add additional amounts of an improver such as potassium bromate to help him to work to a timetable. With all these improvers the amount added is small. Other improvements in bread are produced by the inclusion of glycerinated fats; the product sold in this country as glyceryl monostearate contains about 30% monostearate, the remainder being glyceryl distearate and unchanged fat. There is no evidence that this substance has any toxic hazard and in fact it is present in certain natural fats, including margarine. Dr. Coppock also referred to a new physical method of bread improvement, developed in this country, which does not involve the use of any chemicals. The method is now being closely investigated by research organisations.

Mr. T. MORAN, D.SC., said that the problem should be kept in its proper perspective. The amounts of chemical improver used are small—much less than the chemical additions permitted by law to a wide range of other foodstuffs. Furthermore there is no danger of the amounts being greatly exceeded, because over-treatment ruins the loaf. These improvers are all oxidising agents and act by modifying the elastic properties of the gluten. This action probably includes oxidising the -S-S-linkages between adjoining polypeptide chains. Improvers also neutralise the action of any free glutathione which adversely affects baking quality. Much of the oxidising capacity of improvers is spent on the fat, but obviously it is also possible that many of the constituents of the flour, including a number of amino-acids, will be oxidised. There is thus probably a wide range of reaction products over and above those required for flour improvement. The discovery of the effects of agenised flour in producing running fits in dogs and other animals was a dramatic example of the formation of an extraneous product; the toxic factor, which has been isolated and synthesised, is methionine sulphoximine, and it has no flour-improving action. At the same time it is important to keep the scale of possible changes in mind. If, say, all the agene used in the commercial treatment of flour reacted with the methionine alone, only 3% of this amino-acid would be altered. In point of fact the content of methionine sulphoximine in flour is about 2 p.p.m., so in the course of a year the average person consumes only 2·5 mg. per kg. body-weight. This small amount, coupled with the different detoxication mechanism, explains why agenised flour has no harmful effects in man. All concerned are now considering what should replace agene. Chlorine dioxide is now being used in the U.S.A. and Canada, and biological tests in the U.S.A. have given no reason to suspect that this can be in any way harmful to man or animals. Nevertheless such tests have their limitations, and in order to leave nothing to chance attempts are being made in this country to identify substances formed by the action of chlorine dioxide which are present only in trace amounts.

Prof. A. C. **FRAZER** dealt in detail with the toxicological aspect. He showed how any direct or indirect toxic action can be recognised, and described the safeguards. These include acceptability tests on a wide range of animals with a dose, in the U.S.A., of one hundred times the standard. The residues left by these improvers are negligible; in the case of flour treated with bromate, for example, the finished loaf contains less potassium bromide than is present in normal blood or in good red tomatoes. At the normal commercial levels, on the evidence available, there seems to be no hazard; biological tests were of great value in arriving at this conclusion. The toxic factor formed by the agene treatment of flour would have been recognised had this improver been tested according to the scheme outlined, which in fact has already been applied to chlorine dioxide. He also discussed glyceryl monostearate and polyoxyethylene stearate, and certainly there appears to be no objections to the use of the former.

Professor **MCCANCE** commented on the fact that polyoxyethylene stearate was used at much higher levels in the U.S.A.; while Dr. G. M. **BULL** suggested that the character of the diet, including, for example, its content of cholesterol, would affect acceptability tests in animals. Dr. H. E. **MAGEE** mentioned the uncertainty as to where detoxication of methionine sulphoximine takes place.

New Inventions

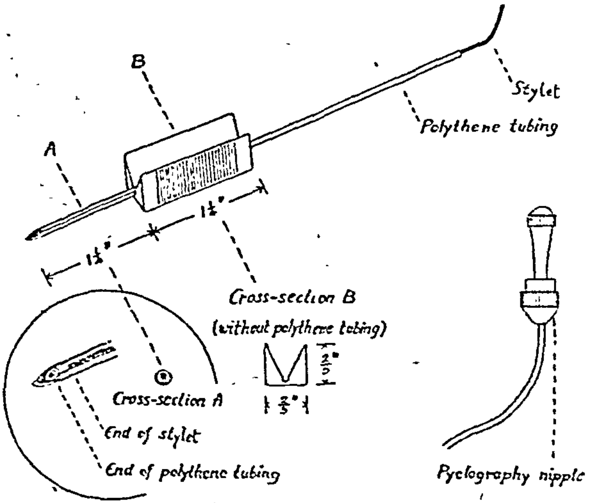
AN INTRODUCER FOR PLASTIC CANNULÆ

To facilitate the insertion of fine plastic cannulæ into veins I have devised an introducer, which for the past year has been used at St. George's Hospital and found satisfactory.

The introducer consists of a gutter needle with its proximal half embedded at the apex of a V-shaped groove in a long metal block acting as a holder.

The gutter is prepared from a needle $2^1/_2$ in. long with a short bevelled point whose lumen will just admit the cannula to be used. In section the gutter is crescent-shaped, its walls describing two-thirds of a circle. The free edges of the gutter are thinned to remove the angular ledge, between plastic cannula and needle, which may lead to the formation of a hæmatoma.

The holder block measures $1^1/_4 \times {}^2/_5 \times {}^2/_5$ in. The V-shaped groove along its length prevents the plastic cannula from being touched by the operator's fingers.



The tip of the cannula to be used is bevelled to correspond to the tip of the needle. To prevent acute bending, which might occlude or break the tube, a thin straight copper-wire stylet which does not protrude at the bevelled tip of the cannula is used. This also facilitates introduction.

The instrument is sterilised by boiling, with plastic cannula and stylet in position.

Any vein which will admit the desired cannula may be used, including those on the dorsum of the hand. The skin is sterilised, the arm is constricted to dilate the veins, and the tip of the needle with tubing in place, is introduced into the vein for a fraction of an inch. The cannula is then advanced along the vein for 2 in. while the constriction is taken off the arm. Next, the cannula is lifted out of the gutter and at the same time the introducer is withdrawn. After this the stylet is withdrawn.

For continuous drip transfusions the cannula is connected to the blood-transfusion set with a pyelography nipple (Thackeray). This makes it possible to use the whole lumen of the cannula. For intermittent injection an ordinary needle can be inserted into the lumen of the tube.

The introducer has been made by A. L. Hawkins & Co. Ltd., 15, New Cavendish Street, London, W.1.

K. BOHEIMER, M.B. LOND.
Late Resident Clinical Pathologist,
St. George's Hospital, London

Reviews of Books

Lung Abscess

R. C. BROCK, M.S., F.R.C.S., F.A.C.S., thoracic surgeon, Guy's Hospital and Brompton Hospital, London. Oxford: Blackwell Scientific Publications. 1952. Pp. 190. 35s.

IN this book Mr. Brock has collected and edited a series of his papers which appeared in *Guy's Hospital Reports* between 1945 and 1948, and has written additional chapters, so as to give a complete description of lung abscess and its treatment.

After a brief description of bronchopulmonary anatomy and a statement of terminology, he goes on to discuss the pathology of lung abscess, laying particular stress on the importance of bronchial embolism. Then follow clinical descriptions of lung abscess arbitrarily divided for the purposes of description into fœtid and non-fœtid abscess. Relevant case-reports are given throughout. Staphylococcal and Friedländer lung abscesses are discussed in separate chapters because their ætiology is different from that of abscesses previously described. There is also a separate chapter on lung abscess in carcinoma (though it seems doubtful whether the breaking down of peripheral carcinomas should be classed as lung abscesses).

Treatment of lung abscesses has changed strikingly in the last few years. With the advent of chemotherapy, they have become much less common; and since penicillin in high dosage often clears them up, the operation of drainage is now rare, and in many chest units has seldom been done during the last 3–4 years. Mr. Brock, however, maintains that drainage still has a very definite place; though he admits the high mortality of the operation. He does not make it quite clear exactly which cases should be drained, but crystallises his own opinion and brings it into line with that of many other surgeons when he says in his last paragraph: "One inclines more and more to the use of lobectomy at an earlier and earlier phase in the treatment of a lung abscess that has failed to respond to expectant treatment."

The illustrations are excellent, and illustrative case-histories have been used to great effect in this eminently readable book.

The World View of Physics

C. F. WEIZSÄCKER. London: Routledge & Kegan Paul. 1952. Pp. 219. 12s. 6d.

THIS remarkable book, ably translated by Marjorie Grene, is written by a natural and moral philosopher, and the ethical level is high from cover to cover. Weizsäcker is like a guide among the peaks of a strange land who is not satisfied to point to their grandeur but needs must ask to what point they pinnacle. To him the Godhead is ever present; and since he is an astrophysicist of high standing this gives point to the claim that though a man can have his feet planted firmly on the ground his gaze may be elsewhere. Weizsäcker seems to be as much at home evaluating the contributions of the moral philosophers down the ages as he is in the fields of experimental and observational physics; so whichever field interests the reader he will find plenty to engage him. It is fascinating to read that Goethe thought Newton had, in a way, degraded sunlight in his experiments, when he allowed only a narrow beam of it to enter the darkened room; yet Newton made the discoveries. The moral philosophers are subjected to a penetrating scrutiny—Leibnitz is rebuked for his levity in remarking that the world is the best of all possible worlds—and the mathematicians are challenged for some of the beliefs they express. The last two chapters of the book are pregnant with the charge that we must all bear the responsibility for what we do, however small it may seem in the sum total of human effort. He, a scientist, cannot look to science for salvation, for, as he says in his closing lines, "what matters is not loveless freedom, nor recognition and reverence of love, but only love itself."

Symposium on Geographic Pathology and Demography of Cancer

Editor: Dr. J. CLEMMESEN, scientific secretary to the symposium. Council for the Coördination of International Congresses of Medical Sciences. World Health Organisation and United Nations Educational Scientific and Cultural Organisation. Paris: Maison de l'Unesco. Pp. 152.

THIS volume includes a report of a conference and symposium held in Oxford in 1950 to review existing information on the endemiology of cancer and to agree on methods for collecting more data and evaluating them. Presumptive evidence that primary cancer of the liver is relatively common in Africa and Indonesia; that cancer of the cervix uteri is relatively uncommon in Jewish women; that cancer of the stomach is uncommon in Javanese, African Negroes, and the indigenous people of French North Africa; that cancer of the base of the tongue is relatively common in certain communities in India; and a few more such correlations between anatomical sites and demographic areas was given by speakers from the territories concerned. Two problems—liver cancer in certain regions, and the rareness of cervical cancer in Jewish women—were selected for special study, to be integrated with work already in hand in the places and on the populations concerned.

Psycho-Analytic Study of the Child

Vol. 6. Editors: RUTH S. EISSLER, M.D., and ANNA FREUD. London: Imago Publishing Company. 1951. Pp. 393. 40*s*.

THIS sixth volume is bigger and more expensive than its predecessors, but also better. Every paper is of a high standard.

Of interest to English workers, who already know his film *Grief*, is Dr. René Spitz's analysis of ætiological factors responsible for different types of behaviour disorders in early life. He distinguishes eight types of unsatisfactory mother-child relationship, finding each responsible for some particular syndrome. For instance "total deprivation" results in marasmus, partial deprivation in "anaclitic depression" (discussed by Dr. Spitz in an earlier volume), "primary anxious over-permissiveness" has as its consequence "three-months colic," and so on. While the critical reader may not accept this absolute one-to-one correspondence, most will concede that Dr. Spitz does establish the importance of the mother-child relationship in the early days and the damage to mental health that is likely to ensue if it is bad. It is important to get this proposition attended to, since much of the care given to mothers and young babies is still based on a highly mechanistic theory of child management.

Miss Anna Freud and Miss Sophie Dann give a most interesting account of twelve months of the lives of six orphans brought to England from Teresienstadt concentration camp. The children had been entirely deprived of home and parents and had started life among people who, though kindly, dared not waste a movement because of their own severe malnutrition. The paper, which throws much light on the essential elements of normal upbringing, also reveals the writers' skill (of which they seem unaware) in handling difficult children.

The criticism to be made of this volume is that it brings together in a somewhat undiscriminating way technical and popular papers. Perhaps it should have been divided into two, one for the professional and one for the general reader.

The Enzymes

Chemistry and Mechanism of Action. Vol. II, part 2 Editors: JAMES B. SUMNER, Laboratory of Enzyme Chemistry, Cornell University, New York; KARL MYRBÄCK, Institute for Organic Chemistry and Biochemistry, University of Stockholm, Sweden. New York: Academic Press. 1952. Pp. 649. $14.00.

THIS, the last of the four parts which make up these two volumes, contains, besides 14 articles, the author and subject indexes to vol. 2. The work as a whole is conspicuous for careful planning and presentation and for the generally high standard of the articles, contributed by about 100 experts.

Among the articles in this last part are those of H. A. Krebs on urea synthesis, K.-B. Augustinsson on acetylcholine synthesis, and S. Ochoa on carbon dioxide fixation. Carbohydrate-fat conversion is described by F. L. Breusch, and there are good chapters on photosynthesis, nitrogen assimilation, and bacterial fermentations. Tumour enzymology is reviewed by J. P. Greenstein and A. Meister of the U.S. National Cancer Institute; they present a concise and discriminating selection from the literature of this subject. The sections on depression of liver catalase and increased serum aldolase activity in cancer subjects are of particular interest. The book concludes with a long article on enzyme technology which will be of value to those concerned in large-scale enzymatic processes, whether to do with alcoholic and other fermentations, the production of antibiotics, or the manufacture of leather.

Osler: The man and the Legend

W. R. BETT. London: Heinemann Medical Books. 1951. Pp. 125. 15*s*.

Dr. Bett has set out to portray Osler through his writings on the topics which most interested him. Having in a short biographical chapter erected his subject on a pedestal, Dr. Bett proceeds to turn it this way and that as one may turn the Venus of Milo in the Louvre. He presents Osler through his writings on typhoid fever, pneumonia, tuberculosis, and—rather particularly—syphilitic aneurysm of the aorta. We see him as the clinician, the teacher, the medical historian, the classical scholar, the bibliophil, the author, and the man. As the examination proceeds with the aid of various spotlights, the figure becomes wondrously alive.

"A great clinician, a fine pathologist, a delightful medical historian and the most engaging of companions particularly to younger men—all these things was Osler." "One of the most interesting things about this extraordinary man was the variety of his interests in clinical medicine. To those specialising in tuberculosis he appeared to be primarily interested in that disease. Yet few of his contemporaries had a wider or more profound knowledge of typhoid fever, of malaria, of malignant endocarditis, of chorea, of abdominal tumours, of cerebral palsies in children, of polycythæmia, of multiple telangiectases and . . . of his two pet subjects—syphilis and aneurysm." At school "Willie Osler was irrepressible and frequently in trouble. On one occasion he locked a flock of geese in the school-room; on another he and his fellow conspirators emptied the school of desks and benches and hoisted them through a trapdoor into the garret, and it is hardly surprising to learn that such escapades and others like them finally led to his expulsion." His love of a practical joke remained with him. "He never tired of confessing that students were the inspiration of his life." Few of them would think that an anatomical text could ever have charm until they read his description of "the area of abdominal romance where the head of the pancreas lies folded in the arms of the duodenum."

A great man, a remarkable man, a lovable man, there has been no-one like him: he has become a legend. Dr. Bett has done his job very well indeed.

THE LANCET

LONDON: SATURDAY, MAY 24, 1952

A Conspectus of Epidemiology

THE wavering ranks of preventive medicine, still somewhat discouraged by the National Health Service Act, were rallied last week by an unusual and heartening experience on the occasion of the presidential address to the newly styled section of epidemiology and preventive medicine of the Royal Society of Medicine. The president, Prof. ROBERT CRUICKSHANK, first achieved distinction as a laboratory worker with interests in the field of communicable diseases; yet he made plain his conviction of the folly of restricting the practice of epidemiology to the use of bacteriological techniques. The methods of epidemiology, he said, could be applied universally; and lest his younger hearers thought that the present expanding interest in the epidemiology of cancer and peptic ulcer, heart-disease, and suicide, was a modern notion, he cited the definition of epidemic disease given by the Epidemiological Society of London in 1862: this included "many local and constitutional diseases which at times assume an epidemic character; and certain endemic and indigenous diseases such as goitre, pellagra and beri beri which are peculiar to regions and countries." Indeed comparison of the incidence of particular diseases in contrasting groups of the population is the essence of the epidemiological method. In this concern with the study of disease in groups rather than individuals, it differs from the two other basic forms of medical discipline. Clinical workers strive to record symptoms and signs with a view to diagnosis, while laboratory research aims either at extending diagnostic powers by means of aids to the senses or at studying the fundamental processes of disease. The epidemiologist in the field, on the other hand, relates disease incidence to the character and race of the people, and the distribution of disease in time to changes in environment and personal habits or in space to the place of domicile or work. But as WADE HAMPTON FROST has pointed out: "Epidemiology at any given time is something more than the total of its established facts. It includes their orderly arrangement into chains of inference which extend more or less beyond the bounds of direct observation."[1] What CRUICKSHANK called the "social post mortem" may be a complex affair in which dissecting and analysing the collected data calls for much statistical tact. Even with communicable diseases due to a specific organism the interaction between host resistance, parasite virulence, and physical environment may be very difficult to disentangle. The recognition by KOCH of the organism causing tuberculosis was merely the end of the beginning in the struggle to control the disease. Host resistance varies with sex, age, and race; but such knowledge in itself does not tell us whether the young Negro in an urban community dies from tuberculosis because he is negroid or because of underfeeding, overcrowding, or some other social correlate of his economic position. Again, environment may have a direct effect on host resistance; thus ARMSTRONG believes that variations in atmospheric humidity reduce the resistance of the upper respiratory mucosa to invasion by the poliomyelitis virus and antedate the onset of epidemics of that disease. Environment also exerts an indirect effect by altering people's habits; a fall in temperature may result in poor ventilation and readier spread of infectious illness. Thus, although it is convenient to separate the three basic components in the ecological balance which determines the incidence of disease, the relationship of host, agent, and environment is both complex and dynamic. Any change in the relative weight of one of these components may change symbiosis into a parasitism dangerous to either parasite or host. Both man and the virus of foot-and-mouth disease are predatory on cattle; hence our present anxiety lest the dangerous parasitism of our rivals may upset the precarious protein balance of our national dietary and set in train fresh epidemics of deficiency disease.

Much has been made by the disciples of social medicine of differences in mortality between the social classes. Extensive surveys, based essentially on vital statistics, have shown that excessive death-rates are associated with the domestic and other circumstances of poverty. Such macroscopic reviews do not, however, allow any confident identification of the major causes within the knot of interrelated variables that include malnutrition, overcrowding, and poor personal hygiene; and CRUICKSHANK believes that the time is ripe for more intensive microscopic studies aimed at isolating and measuring each of these factors in relation to the spread of disease in the home. He feels that in the carefully controlled field trial even the difficulties inherent in the variability of human response to infection can be turned to good account. In the trials of whooping-cough vaccine the difference between inoculated and control groups in the distribution of cases of differing severity clearly showed the advantages of immunisation.

With changing emphasis in the numerical importance of infectious and non-parasitic disease, epidemiological methods are now being applied increasingly in fields other than the traditional one of the acute specific fevers. Surveys of the incidence of cancer of the lung in relation to the classical trilogy of the epidemiological approach—time, places, and persons—highlighted the possible ætiological importance of atmospheric pollution and smoking; and intensive study of the histories of patients with this disease has confirmed the validity of at least the second of these initial clues. Field studies contrasting the incidence of peptic ulceration in varied working groups have proved a healthy corrective to vague clinical impressions of the relevance of occupational differences to causation. Accidents, which are a major source of disability and death in modern civilisation, might not seem a fruitful field for epidemiological inquiry; but two professors of that subject have contributed notably to the knowledge of accident causation. MAJOR GREENWOOD in this country early devised methods for measuring the host factor in accident proneness, while JOHN GORDON in Boston has shown how accidents can be prevented by attention to the environmental circumstances.

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[1] 1. Armstrong, C. *Amer. J. publ. Hlth*, 1950, 40, 1296.

Despite its complexities, epidemiology is essentially a practical science, firmly based on a rigorous statistical discipline, which can give useful leads to the prevention of disease. While it seldom tells us the whole truth, it may tell us some very useful parts of the truth: we need be hardly less confident in declaring that heavy smoking is a dangerous habit than SNOW was in recommending that the handle of the Broad Street pump should be removed.

Ferrokinetics

THE intensive research into atomic energy produces, every now and then, methods that can be applied to medical problems. The details of these methods become ever more complicated, and the point was long ago reached when the ordinary medical research-worker must accept them without inquiring too deeply into their theoretical background.

LAWRENCE and his co-workers in the medical physics laboratory at Berkeley, California, have applied to the study of the distribution of iron in the body an instrument known as the "scintillation counter": a reliable counter of this type was described two years ago by ANGER.[1] This scintillation counter has an efficiency for γ rays fifty-five times greater than similar Geiger-Müller equipment, and this great increase in efficiency has enabled workers to follow the fate of a γ-emitter like Fe^{59} when given in doses well below the toxic level. Furthermore, with the Anger scintillation counter the need for estimations of blood samples or actual tissue samples is largely eliminated; the distribution of a γ-emitter in the intact subject can be accurately estimated by placing the counter over the same situation in the body at different times. In a paper entitled "Ferrokinetics," the team at Berkeley[2] have reported preliminary observations on the distribution and fate of a single intravenous dose of Fe^{59} in normal people and patients with various blood diseases. The sites observed were the liver and spleen; and, for bone-marrow, readings were taken over the sacrum, which was chosen because it provides a relatively concentrated area of marrow near the surface and sufficiently far from interference from the spleen. Judging by the uptake of iron from the blood, the skull and long bones of adults contain little active marrow. The distribution of iron in the plasma and red cells was determined by means of blood samples, and allowance could then be made for the radioactive iron in the blood when estimating tissue activity.

In normal people Fe^{59} injected intravenously is rapidly removed from the plasma, about 90% disappearing in the first 8 hours; no significant amount of iron appears in the red cells for about 2 days, after which it rapidly increases and reaches a maximum about the 6th day. The scintillation-counter method shows that almost all the iron goes directly into the bone-marrow; a little is deflected via the liver, but returns to the marrow; there is no evidence of any accumulation in the spleen in the first 2 weeks. After 10–14 days the iron has mostly left the bone-marrow and is found in the red cells. In two patients with myelofibrosis, confirmed by marrow biopsy, the iron accumulated in the spleen and not in the marrow. One of these patients had myelofibrosis following polycythæmia vera, and she showed no increase of iron in the liver. The other patient was thought to have myelofibrosis with myeloid metaplasia in the spleen, and in this patient iron accumulated rapidly in the liver as well; this is interpreted as showing that erythropoiesis was taking place in the liver as well as the spleen. In a man with an aplastic type of anæmia the iron, as was expected, did not go to the marrow but, surprisingly, accumulated in the liver and appeared to be held there; the iron was slowly released, and only about 10% of the injected dose reached the red cells, compared with the normal 80–100%. Again, in a patient with chronic myeloid leukæmia the iron did not go, as expected, to the marrow, but was equally distributed between spleen and liver. When the tracer began to appear in the red blood-cells, the iron in the spleen was being reduced, but not that in the liver; this suggests that the numerous erythroblasts in the spleen in this disease are actually erythropoietic, while the liver acts only as an iron store. In patients with anæmia and an enlarged spleen two different types of "ferrokinetics" were observed. One type is that mentioned already in the case of myelofibrosis after polycythæmia. The injected iron did not go to the marrow but accumulated rapidly in the spleen; later the spleen iron decreased, and at the same time iron tracer in the red blood-cells increased, suggesting that red cells were being formed in the spleen. This type of response is called "erythrogenic." In the second type the iron went first to the marrow, but when the iron in the marrow began to diminish there was a great and sustained rise in the spleen iron and much less iron than normal appeared in the red blood-cells; this suggests that the red cells were being rapidly destroyed soon after formation, and that their released iron was being accumulated in the spleen. This type of response is called "erythronoclastic." One patient showing this type of response was a man of 72 with refractory anæmia associated with a hyperplastic marrow and without evidence of peripheral hæmolysis —reticulocytes were low, the Coombs anti-globulin test was negative, and fæcal urobilinogen excretion was normal. His spleen was removed, and on section showed hyperplasia of the reticulum and no erythropoiesis. Another patient with this "erythronoclastic" type of response had a definitely hæmolytic type of anæmia associated with multiple myeloma; there was erythroblastic hyperplasia in the marrow, reticulocytosis, and a high fæcal urobilinogen excretion. It has long been suspected that excessive red-cell destruction could occur in the spleen without any of the usual evidence of hæmolysis in peripheral blood, but in these cases splenectomy has usually been avoided because hæmolysis was apparently absent. The observations from ferrokinetic studies, if confirmed, will lead to reconsideration of the nature of these puzzling cases.

These results give a somewhat different picture from that obtained by following the fate of injected iron tracer in rabbits. VANNOTTI,[3] for instance, concluded that in rabbits the liver, and not the bone-marrow, as the site where the injected iron accumulated when first disappeared from the plasma, and it was om the liver that iron was released to the red lood-cells; iron normally only appeared in the spleen 0 days after the original injection, when hæmolysis f the iron-containing red cells was beginning. The ifference in metabolism is presumably a species ifference and is one more warning of the danger of pplying results of animal experiments to function nd dysfunction in the field of clinical hæmatology. he work on rabbits does, however, suggest that it ill be worth while to follow the fate of injected iron racer longer than the two weeks to which LAWRENCE nd his colleagues have so far restricted their studies.

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[1] Anger, H. O. A.E.C. Report, UCRL 885, UCRL 886, Aug. 30, 1950.

[2] Huff, R. L., Elmlinger, P. J., Garcia, J. F., Oda, J. M., Cockrell, M. C., Lawrence, J. H. *J. clin. Invest.* 1952. 30, 1512.

[3] Vannotti, A. *Bull. schweiz. Akad. med. Wiss.* 1946, 2, 90.

Chronic Constrictive Pericarditis

A SUCCESSFUL pericardial decortication for con-trictive pericarditis is one of the most effective measures in modern practice. The results of this operation cannot, however, always be predicted. Older patients, for example, and particularly those with much pericardial calcification, usually prove bad surgical risks because of underlying coronary artery disease and resultant myocardial atrophy. The choice of cases, especially early cases, for pericardectomy is not easy. Ideally the operation should be done before many secondary effects develop. The disorder, it is now clear, results from tuberculous infection; and operation may have to be considered before the signs of active tuberculosis elsewhere in the body have abated [1] Then again, any tamponade effect may be due to pericardial effusion alone without constrictive pericarditis—in either event radiographs show anyhow moderate enlargement of the cardiac shadow [2]—and tuberculous pericardial disease does not always progress to chronic constrictive pericarditis.

The clinical features, confirmed by EVANS and JACKSON [3] in a series of 30 cases, are fairly familiar: cyanosis; small pulse-volume; low blood-pressure; sometimes fibrillation; full neck veins; large liver; dropsy; "dry" lungs; and slight cardiac enlargement, with an adventitious heart-sound. Pulsus paradoxus is on the whole an unreliable sign.[4] The sound of hepatic friction seldom accompanies the extensive perihepatitis of this condition, but may appear after pericardial decortication when the liver is shrinking.[5] Sometimes pulsation of the liver is evident, suggesting tricuspid stenosis [6]; and mitral stenosis is often simulated radiologically by apparent left auricular enlargement. Rarely the mitral ring may even be invaded by fibrosis and calcification penetrating deeply from the pericardium into the auriculoventricular fissure. Distinction from mitral stenosis should, however, be possible by studying the response of cardiac output to acceleration of the pulse; in mitral stenosis cardiac output varies inversely with the rate of the heart, whereas in constrictive pericarditis the two are directly related. The syncopal attacks sometimes noted in constrictive pericarditis probably reflect the failure of cardiac output to increase adequately in response to effort. Breathlessness on movement is an important symptom, and when pronounced probably indicates some measure of constrictive pleural thickening. In contrast, orthopnœa is usually absent despite the very high venous and cerebrospinal-fluid pressures. Possibly the sensorium is clouded in these patients, so that they are less troubled by symptoms than others.[7] The absence of pulmonary congestion, however, is a notable factor. EVANS and JACKSON emphasise the diagnostic value of electrocardiographic changes. In their cases with low or flat T waves the pericardium at operation stripped easily from the heart; but deep T-wave inversion implied penetration of the myocardium by the pericardial inflammation, and decortication proved impossible. They suggest that in difficult cases liver biopsy should be done to determine the state of the enlarged liver. Radiographically pericardial calcium is seen in over half the cases, mainly on the diaphragmatic surface of the heart, like an egg-cup holding it [3]; the apex, however, is often free.[5] Angiocardiography has not proved helpful, but kymography may be informative.[8] The characteristic "flat top and V" pattern of the electrokymogram is said to be diagnostic of chronic constrictive pericarditis.[9] These curves show also that the protodiastolic heart-sound commonly heard is caused by rapid ventricular filling abruptly halted, giving a kind of water-hammer effect. Abnormalities are constantly revealed by the ballistocardiogram, which is also helpful in correlating surgical results. The ventricular filling of the rigidly encased heart, abruptly terminated in early diastole, gives rise to large diastolic ballistocardiographic waves which disappear after pericardectomy.[10] Cardiac catheterisation has similarly shown a fairly characteristic pattern for right ventricular pressures.[11] Abnormalities of the serum-proteins in this condition are not closely related to the extent of liver congestion, and electrolyte studies have suggested that the fluid and salt retention may be more closely connected with adrenocortical activity than with the venous hypertension.[12]

With regard to treatment, BLALOCK [13] emphasises that both sides of the heart must be decorticated; and his approach, which enables this to be done, is by a left anterolateral transpleural incision in the 4th interspace, dividing the 4th and 5th costal cartilages. The reproduction of pericardial constriction in dogs by suturing plastic casts within the pericardium has shown clearly that constriction of the auricles is of little importance in the syndrome, and that the mechanical handicap results specifically from constriction of either or both ventricles; and liberation of both ventricles, with total excision of the pericardial scar, is the essential aim in operating.[14] Excellent as the results have been, we must not forget that this disorder is the late effect of a localised tuberculous infection. Each year our attitude towards tuberculosis becomes more aggressive; and with more effective prevention chronic constrictive pericarditis may become rare.

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1. See *Lancet*, 1951, ii, 392.
2. *Ibid*, 1949, i, 788.
3. Evans, W., Jackson, F. *Brit. Heart J.* 1952, 14, 53.
4. Dornhorst, A. C., Howard, P., Leathart, G. L. *Lancet*, April 12, 1952, p. 746.
5. McKusick, V. A. *Bull. Johns Hopk. Hosp.* 1952, 90, 3.
6. Wenckebach, F. K. *Brit. med. J.* 1907, i, 63.
7. Altschule, M. D. Physiology in Diseases of the Heart and Lungs. Cambridge, Mass., 1949.
8. McKusick, V. A. *Bull. Johns Hopk. Hosp.* 1952, 90, 27.
9. Gillick, F. G., Reynolds, W. F. *Radiology*, 1950, 55, 77.
10. Scarborough, W. R., McKusick, V. A., Baker, B. M. *Bull. Johns Hopk. Hosp.* 1952, 90, 42.
11. Mansen, A. T., Eskildsen, P., Gotzsche, R. *Circulation*, 1951, 3, 88.
12. Davis, J. O., Lindsay, A. E., Southworth, J. L. *Bull. Johns Hopk. Hosp.* 1952, 90, 64.
13. Blalock, A. *Ibid*, p. 1.
14. Isaacs, J. P., Carter, B. N., Haller, J. A. jun. *Ibid*, p. 259.

Annotations

FOOT-AND-MOUTH DISEASE

THE epidemic of foot-and-mouth disease has already lasted seven months, and, apart from a brief mid-winter respite, has shown little sign of abating. Traditional invasion areas in the eastern and southern counties have borne the brunt of the attack, but Cheshire, Wales, and Scotland are also suffering severely. Over 300 outbreaks have meant the destruction of some 19,000 cattle, 12,000 sheep, and 7000 pigs—figures which make plain the loss of milk, meat, and money, but not the elimination of many valuable pedigree herds. The official policy of slaughtering all affected animals and their contacts seems at present to be having little effect on the number of outbreaks; and the farmer, behind his disinfectant moat, may soon begin to doubt its wisdom. In the years 1941–51, when outbreaks of the disease were small and the average annual cost of compensation to farmers was £220,000, the policy worked well, but the scale of the present epidemic imposes a test whose outcome will affect us all. Economic as well as epidemiological considerations must shape policy; and it should be remembered that in Germany, where the disease is controlled by isolation and vaccination, the 1937–38 outbreaks cost over £80,000,000.

In this country we normally maintain a precarious freedom from foot-and-mouth disease; the Channel is our main defence, but import restrictions also help. The present outbreak undoubtedly sprang from the epidemic which started in Germany in the summer of 1951 and which, by early winter, had reached the Low Countries and France. On the Continent the disease smoulders endemically and occasionally flares up; last winter Germany, for example, had 20,000 new outbreaks a month. The disease in Britain closely reflects the state of affairs on the Continent, but there is an important epidemiological difference. Continental epidemics may be simply peaks in a curve of endemic prevalence, whereas our outbreaks start from a base-line of freedom from infection. Slaughtering all cases and contacts is a reasonable policy only if we can be sure that the disease is not already widely disseminated among the animal population. There seems little doubt that these conditions are fulfilled in this country, though it is possible that subclinical infection may occur; this would be extremely difficult to detect except by such methods as the newly developed complement-fixation test. Slaughter must be ruthlessly carried out if it is to eradicate each focus of infection and prevent the farm-to-farm spread by which the disease could quickly become endemic. The attack on the present epidemic must be judged in this light, and we have an assurance that in a high proportion of outbreaks there has been no evidence of secondary spread.[1] The present epidemic may therefore be regarded as a series of outbreaks most of which have had an external source of infection; there have, of course, been secondary cases, but this is not the usual method of spread. Such a view certainly fits in with the early history of the epidemic; and although it is notoriously difficult to trace chains of infection in any virus disease, it may still hold. If so, then the present policy is abundantly justified; it gradually brings the epidemic under control as the Continental outbreaks subside. We have already referred[2] to the carriage of the virus on the feet and feathers of migrating starlings, pigeons, and other birds; and though it is virtually impossible to prove that they are the chief culprits, circumstantial evidence during the present epidemic has been very strong. Two main bird migrations are southwestwards from the Low Countries in autumn and north-eastwards from France in the spring. Outbreaks of foot-and-mouth disease in Holland and North Germany, which normally take place in the autumn, have usually died down by the time the birds return from France in the spring. But the epidemic continued this year, and the time during which infected birds could introduce the virus into this country has been unusually long.

Critics of the slaughter policy usually point out that vaccines have been used in Mexico and elsewhere with considerable success. Unfortunately the position is complicated not only by the three immunological types (A, O, and C) of the virus, but also by at least six variants within type A. As with influenza in man, a vaccine must be prepared from the prevailing type of virus if it is to be effective; polyvalent vaccines have, so far, been of little value. The immunity which can be induced by vaccination probably lasts about 6 months, so frequent revaccination would be necessary. Some workers believe that the partial immunity which vaccination may give carries the risk of subclinical or mild infections which would allow the virus to spread far before it could be recognised. These reasons, together with the expense of producing the vaccines, and the fact that they have not controlled the Continental epidemic, should make us hesitate to advocate their general use in this country. Indeed vaccination and isolation appear poor alternatives; and if they were adopted, the disease would almost certainly become endemic with periodic epidemic waves—a state for which we would have no remedy. The present epidemic is undoubtedly persistent, but we should remember that in 1923 there were 1853 outbreaks and 125,000 animals were destroyed before the infection was brought under control. Many other countries pursue policies like our own, but prevention should obviously be organised on an international basis. Meanwhile we can best serve our own interests and those of other countries by continuing to support the present methods of eradicating the disease.

MORE ABOUT THE THYROID HORMONE

IN recent months Gross and Pitt-Rivers[1] have enlivened our columns with a biochemical serial of great interest to all concerned with the workings of the thyroid gland. Starting with the identification of a new iodine-containing compound in human serum, they went on to show that this substance—triiodothyronine—possessed a high degree of hormone-like activity. Other compounds related to thyroxine are similarly active, but only when administered in large doses. In the test they used (the suppression of thiouracil goitre in rats) triiodothyronine was actually more potent than thyroxine. The goitre-suppression test is a convenient and relatively accurate method of assaying substances for thyroid-hormone-like activity, but a positive result does not necessarily indicate that the substance in question has the same action as thyroxine on tissue metabolism: essentially it is a test of the substance's ability to prevent the anterior pituitary gland from secreting excessive amounts of thyrotropin.

Much time and effort have been given to devising laboratory procedures for assaying the effect of thyroid hormone on metabolism and growth. Many of these procedures have proved valuable, but none has surpassed the test-object provided by Nature in the myxœdematous patient. In this issue the same workers, with W. R. Trotter, describe the effect of triiodothyronine in two cases of myxœdema treated at University College Hospital. The new compound, injected in doses of up to 80 µg. daily, produced an unmistakable clinical response. There was also a sharp fall in body-weight and plasma-cholesterol, and the basal metabolic rate rose to a normal level. The patients' response was what might have been expected from treatment with sodium L-thyroxine in

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[1] *Vet. Rec.* 1952, 64, 277.
[2] *Lancet*, Feb. 9, 1952, p. 299.

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[1] Gross, J., Pitt-Rivers, R. *Lancet*, 1951, ii, 766; *Ibid*, March 1, 1952, p. 439; *Ibid*, March 22, 1952, p. 593. See annotation, *Ibid*, p. 600.

a dosage of about 100–300 µg. daily, or with *B.P.* thyroid extract gr. 1–3 daily. Dr. Gross and his colleagues cautiously refrain from claiming that they have shown triiodothyronine to be more potent than thyroxine in man, but it is obviously an extremely active substance; and so far all the evidence tends to support their suggestion that thyroxine has to be converted to triiodothyronine before it can exert its characteristic effect on metabolism.

The thyroid hormone has been thought to consist of different substances—thyroglobulin, thyroxine polypeptide, thyroxine itself. It now seems likely, however, that triiodothyronine has a better claim than any of these to be regarded as the hormone. Although not contributing anything directly to practical therapeutics, this new work is likely to give fresh impetus to all aspects of thyroid research; and from any substantial advance in fundamental knowledge the clinician stands to gain in the long run.

CYSTICERCOSIS CEREBRI

The diagnosis of cerebral cysticercosis is likely to remain largely a clinical matter until specific sensitisation or serological tests become more reliable. It is therefore important that the clinical pointers to this diagnosis should be widely known. The work of MacArthur[1] and his colleagues in this country established that cysticercosis was an important cause of epilepsy in those without constitutional predisposition who had lived in countries where cysticercosis is common—notably the Far East. This work also showed that in a large proportion of cases the diagnosis had to be made on circumstantial evidence —a history of residence in the East, the presence of cysticerci in subcutaneous tissues or muscles, eosinophilia, and the pattern of the epilepsy. Unfortunately even this evidence is often absent or hard to obtain. Cysticerci in soft tissues may be invisible and impalpable—though really thorough search will often reveal them—and they may calcify, and so become recognisable by X-ray examination, only some time after they have died, though producing their maximum toxic effects on the brain before this. Eosinophilia is inconstant; and the diagnostic pattern of the fits—attacks with multiple or changing focal features, from multiple cysts causing disparate epileptogenic foci—is by no means universal. Indeed infestation may occur in such a way that a collection of cysts presents primarily as a single localised tumour, or gives rise to a diffuse meningeal reaction or interference with normal circulation of the cerebrospinal fluid (C.S.F.) Sometimes there is a rise in C.S.F. protein, or a pleocytosis which may be lymphocytic, partly polymorphonuclear, or even predominantly eosinophilic; but the fluid is often normal. In some countries, such as Italy, skin sensitivity to a cysticercosis antigen is used in diagnosis. This test has never been widely employed in Britain; and the evidence for or against its reliability is still incomplete. Diagnosis therefore depends very much on bearing in mind the possibility of cysticercosis in a patient who has lived in the East and has developed unexpected neurological abnormalities, especially epilepsy, in adult life.

The difficulties are well illustrated by the report[2] of a case of racemose cerebral cysticercosis—a form where the cysts occur in branched clusters of "delicate grape-like bladders." A woman who had lived for many years in India began to have episodic headaches and recurrent bouts of drowsiness or loss of consciousness followed by confusion. She had at least one grand-mal attack, and over a period of years showed increasing mental deterioration, with papillœdema, unsteadiness of gait, and much involuntary choreiform movement. Her C.S.F. was known to have been abnormal in both protein and cell content throughout this period, but she refused ful neurological investigation until shortly before she died. Severe generalised dilatation of the ventricles at this time led to exploration of the posterior fossa, which revealed a large racemose mass over the lower end of the fourth ventricle. Necropsy showed extensive basal arachnoiditis and small nodules diffused throughout the hemispheres and basal ganglia, with a more striking cystic lesion in the head of the left caudate nucleus. These diffuse and focal lesions were well reflected in the patient's clinical state. Bickerstaff et al., who describe this case, point out that the racemose form usually attacks the basal parts of the brain; and, like others, they question whether cysticercosis is as rare as seems to be generally supposed. Their case demonstrates that infestation may give rise to generalised disease of the brain, with clinical features suggesting one or more localised lesions or more diffuse involvement of cerebral function by way of C.S.F. obstruction or primary encephalopathy. It is worth noting that gradual mental deterioration, perhaps with epilepsy and nothing much in the way of localising signs, could readily be produced by one or other of these mechanisms. The consequent diagnostic difficulties hardly need emphasising. Sensitivity tests should perhaps be re-explored.

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[1] MacArthur, W. P. *J. roy. Army med. Cps*, 1934, 62, 241.

[2] Bickerstaff, E. R., Cloake, P. C. P., Hughes, B., Smith, W. T. *Brain*, 1952, 75, 1.

GERMAN MEASLES IN THE ADULT

ONE of the biggest outbreaks of rubella recorded in England is now at its height. In Manchester, the only area where it is notifiable, 4980 cases were notified in the first 17 weeks of 1952—more than in any whole year since 1930, when the records began. Hitherto, the highest annual totals have been 3700 in 1944, 3500 in 1940, and 2800 in 1941. The risk of defects in infants whose mothers contract rubella within 100 days of conception makes the age and sex distribution important. In Manchester, the outbreaks of 1940 and 1944, but not 1941, were remarkable for the high attack-rates in women of childbearing age.[1] So far, the 1952 figures (see p. 1073) show only slight signs of this disproportion.

The clinical picture of epidemic rubella in adults, as described by Bennett and Copeman[2] among the B.E.F. in France in 1940, and later by Gregg[3] and Swan et al.[4] in Australia, differs so widely from the accounts based on children that the diagnosis may well be missed unless children with the typical condition provide a clue. Instead of a trivial ailment, with slight upper respiratory catarrh, slight pyrexia and headache, enlarged sub-occipital glands, a pink macular rash that is often the first sign of illness, and complete recovery in three days, adults may get a more severe and longer illness. Rheumatic symptoms, ranging from transient joint and muscle pains to lumbago, sciatica, and rheumatic-fever-like arthritis, are the main features, usually appearing on the 2nd or 3rd day and lasting up to a week. Others are a follicular tonsillitis, often surprisingly obvious compared with the degree of sore-throat; an intense aching of the gums, mistaken by the patient for toothache, starting at the onset or on the 2nd day and lasting up to 48 hours; generalised enlargement of lymph-glands with leucopenia and relative lymphocyte preponderance; conjunctivitis with well-marked puffiness of the lower lids; and a macular or pleomorphic rash followed by peeling, especially on the hands, as intense as that after scarlet fever. A secondary rise in temperature a couple of days after apparent recovery is not uncommon, but there seem to be no serious complications and the only troublesome sequela, apart from those where a fœtus is involved, has been "rheumatism," which may last for several weeks.

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[1] Clayton-Jones, E. *Lancet*, 1947, i, 56.

[2] Bennett, R. A., Copeman, W. S. C. *Brit. med. J.* 1940, i, 924.

[3] Gregg, N. McA. *Trans. ophthal. Soc. Aust.* 1941, 3, 35.

[4] Swan, C., Tostevin, A. L., Moore, B., Mayo, H., Barham Black, G. H. *Med. J. Aust.* 1943, ii, 201.

ABDOMINAL PREGNANCY

ECTOPIC gestation occurs once in about a hundred pregnancies; but less than 1% of ectopic embryos reach the stage of viability by becoming established in the abdominal cavity, so the incidence of abdominal pregnancy is 1 in about 15,000 pregnancies. Abdominal pregnancy is commoner over the age of 30 and in first and second pregnancies; and it has taken place twice in the same patient.[1] The maternal mortality is about 15%,[2] but is steadily falling with earlier diagnosis, enlightened surgery, and modern resuscitation and chemotherapy. The fœtal loss is extremely high with the increased risk of congenital abnormalities due to adverse environmental factors. Dorman[3] delivered a normal girl of 5 lb. 6 oz. with a smooth postoperative course. In one of Cunningham's[4] cases there was a live child weighing 4½ lb. lying free in the peritoneal cavity with no sac or liquor amnii. In most cases abdominal pregnancy results from tubal pregnancy: the trophoblast erodes through the wall with the placenta retaining its attachment to the tube as the ovum is extruded into the peritoneal cavity, where it becomes secondarily attached. Rarely it may arise in the ovary, or be extruded through a ruptured uterus.[5] There is little doubt that primary abdominal pregnancy is possible,[6] and the fertilised ovum has passed through an opening in the scar of a previous cæsarean section.[7]

Diagnosis should not be too difficult if the possibility is remembered; but the condition is seldom recognised before operation. Dorman[3] describes a case in which there was, as is usual, early tubal erosion with pain and slight vaginal bleeding which was diagnosed as a threatened abortion. Pregnancy proceeds with numerous vague pains and nausea, flatulence, constipation, or diarrhœa from peritoneal irritation. The abdominal swelling may be asymmetrical, and no intermittent contractions will be felt. The cervix is small and firm and may be pushed to one side, and the uterus may be felt apart from the mass. In the last weeks of pregnancy the fœtal movements become painful, and the fœtus itself may be very easily felt unless there is a thick capsule of omentum and intestine. It lies high and oblique or transverse and is tender on palpation; there are no uterine contractions and no round ligaments passing down in front of the fœtus. The presenting part cannot be felt through the cervix as is normally possible, and a sound can be gently passed into the uterus. Soft-tissue radiography of the abdomen will confirm the abnormal position of the fœtus, and the position of the uterus can be demonstrated by a hysterogram or a sound in the uterus. Eventually spurious labour will start with pains and bleeding from the separating decidua. The cervix may open but is never taken up. The fœtal movements may be excessive and then stop; the liquor is absorbed; and the abdominal mass gradually shrinks. The fœtus eventually becomes mummified or calcified, or undergoes adipocerous transformation and may be retained for years; but it may become infected and rupture into a hollow viscus or through the abdominal wall.

Treatment raises some interesting problems. Should operation be delayed to allow the child to develop further? If the diagnosis is made late in pregnancy and the fœtus is alive, it is justifiable to wait till two weeks before term provided the patient is kept in hospital; immediate interference will be safer if careful watch is impossible. Certainly if the fœtus is dead operation should not be deferred in the hope that the placental site will become less vascular; operation should follow soon after diagnosis, and as bleeding may be very severe a saline drip should be running with cross-matched blood at hand. When the fœtus is alive it is unwise to explore the placental site very thoroughly; for partial separation may occur with profuse bleeding, and damage may be done to the mesentery. On the rare occasions when the placenta is circumscribed and attached to some removable organ, such as the uterus, it may be removed, as in Dorman's case. It is usually wiser to divide the cord close to the placenta and close the abdomen without drainage. The retained placenta may take four years or so to disappear, and it may become infected or cause intestinal obstruction. If the fœtus is dead, and especially if it has been dead some time, the placental site will be much less vascular, and it may be possible to remove the placenta. Marsupialisation and packing are not satisfactory and should only be done with gross infection of the sac.

TUBERCULOSIS AND DIABETES

MOST workers believe that in a diabetic tuberculosis tends to be of a fulminating type, and that the diabetes associated with active tuberculosis is particularly difficult to stabilise. Lawrence,[1] however, has expressed the view that, with proper and continuous control of the diabetic condition, tuberculosis is no more to be feared in a diabetic than in anyone else; and from a study of mortality figures he found that diabetics were not dying from tuberculosis to a greater extent than were non-diabetics. There is also a general belief that diabetes predisposes to tuberculosis. For this there is little factual evidence; and full investigation of it would involve a case-finding survey for both tuberculosis and diabetes in a large population, which would then be analysed in the four groups—normal, tuberculous, diabetic, and tuberculous diabetic. Only in this way could undue predominance of the fourth group be satisfactorily established. Boucot and her co-workers[2] in Philadelphia have approached the problem by a tuberculosis survey among diabetics. Their object was to compare the prevalence of radiologically detectable tuberculosis in diabetics with that in a group of normal people similarly examined by mass radiography. Ready access to radiographic examination of the chest was provided for diabetics attending clinics or practitioners in Philadelphia—the majority of those actually examined were referred by diabetic clinics. Boucot et al. calculate that approximately one-third of the diabetics in the city were examined. Obviously, as these workers admit, selective factors may have operated. One such factor is the inclusion in the diabetic group of known cases of tuberculosis, which were presumably not examined in the much larger mass-radiography series. If these known cases are excluded, the prevalence of all types of tuberculosis in the diabetic group is reduced from 8·4 to 6·8%; but it is still significantly greater than the 4·3% found in the non-diabetics. Another possible selective factor, not considered by the Philadelphia workers, is the relation between the percentage of the available population attending for examination and the prevalence of tuberculosis found; Bradbury[3] found in Lancashire that these were directly related. Boucot et al. do not give the percentage response for either series, but it was probably higher in the diabetic group, who were all under medical supervision and were referred for radiographic examination by their physicians. Taking into account these factors and possible differences in the socio-economic background of the two groups, this Philadelphia study does not firmly establish that the prevalence of tuberculosis is necessarily higher in diabetics than in others;

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1. Mitra, S. *Amer. J. Obstet. Gynec.* 1948, 55, 218.
2. Ware, H. H. jun. *Ibid*, p. 561.
3. Dorman, D. B. *New Engl. J. Med.* 1951, 245, 207.
4. Cunningham, J. F. *Irish J. med. Sci.* 1939, p. 846.
5. Gepfert, J. R. *Amer. J. Obstet. Gynec.* 1939, 37, 466.
6. Studdiford, W. E. *Ibid*, 1942, 44, 487.
7. King, E. L. *Ibid*, 1932, 24, 421.

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1. Lawrence, R. D. *Tubercle*, 1948, 29, 253.
2. Boucot, K. R., Cooper, D. A., Dillon, E. S., Meier, P., Richardson, R. *Amer. Rev. Tuberc.* January, 1952, part 2.
3. Bradbury, F. C. S. *Lancet*, 1948, ii, 293.

ertainly it would appear that any difference in prevalence s comparatively small, and would not justify the liversion of mass-radiography units to examine this special group.

Boucot et al. also record a sudden drop in the prevalence of tuberculosis in middle age in white male diabetics. It was found, too, that several relationships between prevalence of tuberculosis (especially active tuberculosis) and diabetes were valid only for the under-40 age-groups. Thus, in those under 40 years the prevalence of tuberculosis was related to the duration and severity of diabetes, and also to a history of coma; whereas over the age of 40 these relationships were not evident, although in this group, as in the younger group, the prevalence of *active* tuberculosis was related to severity of diabetes.

Both tuberculosis and diabetes tend to be acute in young adults, and chronic in older people. The Philadelphia study shows that there is little interaction between the two diseases in later life; indeed, as Boucot et al. point out, in a considerable proportion of these cases the diabetes is probably antedated by the tuberculosis, which may have healed satisfactorily before the onset of diabetes. Any interaction between the two diseases is manifested mainly in the more acute forms in early adult life; and, so far as this age-group is concerned, the American results support the traditional view.

TREATMENT OF VITILIGO

In vitiligo some areas of skin fail to form pigment despite the presence of numerous apparently normal Masson's clear cells. Bloch[1] found that melanin-forming cells contain a dopa-oxidase which converts "dopa" (dihydroxyphenylalanine) into melanin. (Dopa is identical with, or closely related to, the propigment of the skin.) It seems that in vitiligo Masson's cells fail to form dopa-oxidase. This disorder is usually regarded as a trophoneurosis in which the melanoblasts do not function properly because of some disturbance in their autonomic control. Haxthausen[2] found that normally pigmented skin lost its pigment after being transplanted to an area of vitiligo; and, conversely, vitiliginous skin transplanted to an area of normally pigmented skin became repigmented. From this he concluded that vitiligo was not due to a local factor, to vascular abnormality, or to endocrine causes.

Treatment has always been most unsatisfactory. Application of a 10% alcoholic solution of bergamot oil, followed by ultraviolet irradiation, has sometimes led to repigmentation. The application of thorium-X, which often leads to deepening of pigmentation, has been recommended. Some favour gold injections; but in such a harmless condition as vitiligo the use of gold is perhaps unwise because of the risk, however slight, of a serious toxic eruption. With many patients the best advice has seemed to be to ignore the condition except for special occasions, when a weak solution of walnut juice or permanganate could be applied in an attempt to match the pale areas with the surrounding skin.

Encouraging reports have lately come from Egypt[3] on the effects of oral and local treatment with extracts of the seeds of a plant, *Ammi majus* Linn. This plant has been known to the Arabs since the 13th century for its value in vitiligo. A powder made from the seeds was swallowed, after which the leucodermic patches were exposed to the sun. An acute erythematous and vesicular dermatitis usually developed and was followed by repigmentation. Unfortunately, in its crude form, the drug may cause diarrhœa, vomiting, nephritis, hepatitis, or exfoliative dermatitis, which may be fatal. In 1948 Fahmy and Abu Shady[4] reported the isolation from the crude product of three substances: ammoidin, ammidin, and majudin or bergapten. This last substance is present in large amounts in bergamot oil, a recognised light-sensitiser. El Mofty states that of 26 cases treated and followed up for twelve months, the results were excellent in 6, good in 7, moderate in 7, and negative in 6. This compares very favourably with all past treatments, which could be relied on to succeed in only some 2–5% of cases. Body lesions responded better than those on the hands, feet, or genitalia. Failures were more common in the older patients. Repigmentation may begin within a week, or be delayed; it may take place in a punctate and perifollicular fashion, spread in from the margin, or be diffuse from the start. These changes are very well illustrated by Sidi and Bourgeois-Gavardin.[5] Relapses may take place in partly treated areas but not in those that have been cleared completely. No serious toxic reactions have been observed. Tzanck et al.[6] have also reported relief of 7 patients treated with four tablets a day, each containing 10 mg. of ammoidin and 5 mg. of ammidin, or daily painting with a solution containing 7·5 mg. of ammoidin and 5 mg. of ammidin per ml. of alcohol, together with solar or ultraviolet irradiation. Inflammatory reactions were minimal from the internal treatment, but sometimes was pronounced from the local applications.

Irradiation is an essential part of the treatment. It seems that the local application or the oral administration of the drug affects the skin or the autonomic system in such a way that the melanoblasts once again respond to sunlight by forming melanin. The mechanism remains unexplained.

ATTEMPTED SUICIDE

For the first time since its foundation in 1912 the psychiatric section of the Royal Society of Medicine, on May 13, considered the subject of suicide. Dr. E. Stengel remarked that psychiatrists tended to leave this subject to the sociologists. The work of Durkheim,[7] on the sociological and economic aspects, remained a classic; similar work had been done more recently by Swinscow.[8] Psychiatrists were usually more interested in the psychopathology of suicide, which cut across the clinical boundaries of the various mental diseases. Freud's theory of the "death instinct,"[9] though by no means universally accepted, was the most striking contribution to modern ideas on suicide. One reason for the relative dearth of research into this subject was that "dead men tell no tales".

The tendency was to regard patients who failed in attempted suicide as bunglers who had not achieved their object; but, in Dr. Stengel's opinion, this was largely incorrect. The suicidal attempt was often an end in itself, representing a desperate bid (often mainly unconscious) to appeal to society for help in an intolerable situation. It might be regarded as a means of making contact with the group. His own research was on 138 patients admitted in 1946–47 to an observation unit at a London hospital. Usually more women than men attempted suicide, but in this series there were 70 men and 68 women. The most usual method of suicidal attempt had been sedative drugs (25%), while the next most common means were coal-gas and wounding. The Metropolitan police figures for attempts at suicide by sedatives had risen significantly since 1948, and Dr.

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[1] Bloch, B., Schnaf, F. *Biochem. Z.* 1925, 162, 181.
[2] Haxthausen, H. *Acta derm.-venereol., Stockh.* 1947, 27, 352.
[3] El Mofty, A. M. *J. R. Egypt. med. Ass.* 1948, 31, 651; *Ibid,* 1952, 35, 1.
[4] Fahmy, I. R., Abu Shady, H. *J. Pharm. Pharmacol.* 1948, 21, 449.
[5] Sidi, E., Bourgeois-Gavardin, J. *Pr. méd.* 1952, 60, 421.
[6] Tzanck, A., Sidi, E., Bourgeois-Gavardin, J. *Bull. Soc. méd. Hôp. Paris,* 1951, 67, 1400.
[7] Durkheim, E. Le Suicide. Paris, 1897.
[8] Swinscow, D. *Brit. med. J.* 1951, i, 1417.
[9] Freud, S. Beyond the Pleasure Principle. London, 1920.

Stengel wondered whether this was due to these drugs being more readily procured since the inauguration of the National Health Service. If this were so, many who had attempted suicide owed their lives to the N.H.S., for sedatives were a relatively inefficient method of suicide. In his experience, the genuine suicide usually succeeded at the first attempt. Of the 138 patients in his series, only 1 subsequently committed suicide. Most (100) were sent to mental hospitals; 27 were discharged to their homes; and the remaining 11 either died or were transferred to general hospitals. In the four years since their admission to the observation unit, 24 men and 10 women had died from natural causes; 6 men and 4 women had remained in mental hospitals; and 1 man and 6 women were still in mental hospitals after readmission there. The most striking feature about these patients was their relative isolation in the community; 22% of them were living alone, compared with 6% in the general population. Only 9% were motivated by awareness of physical illness. About half of them were vaguely aware that to commit suicide was against the law, but these said that at the time this factor carried no weight with them. Only 43 of them were brought to the notice of the police, who brought 12 to the observation unit; none was charged.

The importance of the patient's isolation was confirmed by Dr. P. Sainsbury from his study of 400 successful suicides. Dr. T. C. N. Gibbens said that the tendency for the police to take proceedings fluctuated somewhat with the number of attempted suicides. Nowadays only about 0·5% were sent to prison, and the maximum sentence was six months. Since the late war, about half of the cases brought to court were dealt with by probation. He cited with approval an opinion voiced at a meeting of the Howard League by Prof. Glanville Williams, that these cases should be brought before the court as adults in need of care and protection, just as children could be brought before a juvenile court for that purpose.

As Dr. Clifford Scott pointed out, suicide, attempted suicide, and violence towards others are all different manifestations of hate and aggression. The patient's attempt at suicide is often aimed at dominating, alarming, or spiting his family or society at large; but the element of guilt and self-reproach about this may well account for some of the successful attempts. Dr. Stengel described attempted suicide as Janus-like, in that it faces towards death and destruction on the one side, and towards life and renewal of human contacts on the other. Possibly this is another way of saying that these patients are in a highly ambivalent position between their impulses of hate and of love.

PREVENTION OF THROMBOSIS IN THE CALF

"SILENT" clotting in the deep veins of the legs, the recognised precursor of pulmonary embolism in immobilised patients, is often difficult to detect, and its prevention is therefore doubly important. Of the many factors predisposing to insidious phlebothrombosis stasis of blood in the veins seems the most significant. In active exercise, both the squeezing effect of muscular contraction and the suction resulting from deep breathing aid the return of venous blood to the chest; and it may derive a further impetus from the vigorous arterial pulse and the pull of the contracting right auricle. When the venous valves are incompetent or there are varicose dilatations of the deep calf veins, which are fairly common in older people, an efficient blood-flow from the legs is even more dependent on exercise, and sudden confinement to bed may be disastrous.

Fractures and other severe injuries in the legs are a recognised cause of deep venous thrombosis and pulmonary embolism. But Crane[1] has lately drawn attention to a paradoxical thrombosis after minor injuries or simple muscular strain. He describes four cases of calf thrombosis in students aged 19–24 after an exercise-tolerance test in which they stepped up on a platform 15 inches high and down again every 4 seconds for 5 minutes. The clinical picture was almost identical in each case—a dull aching in one calf beginning a day or two after the test, local tenderness and swelling, œdema of the ankle, and pain on dorsiflexion of the foot. With rest and elevation of the leg the condition cleared up in about a week. In nine further patients aged 27–70, one of them a woman, the symptoms began during or after playing some game, running for a train, jumping, or kneeling down. Most of these had an acute onset—"something seemed to give way" in their calf muscles. Only one patient, a woman of 70, developed a pulmonary infarct, and Crane emphasises the rarity of pulmonary embolism after this kind of thrombosis. He advises rest in bed, with elevation and compression bandaging of the leg until symptoms and signs have subsided. In tall men, Naide[2] has lately reported 6 cases of spontaneous venous thrombosis of the calf developing after unaccustomed strain; these thromboses seem to be of a particularly dangerous type, their first symptom being pulmonary infarction. Thrombosis on effort in the legs may arise in the same way as the more common clotting in the axillary and subclavian veins, and both may be associated with congenital venous abnormalities.

A pressure of 10–15 mm. Hg applied to the outside of the leg will accelerate the deep venous blood-flow in the limb, presumably by reducing the calibre of the veins, since the velocity of flow in a vein is inversely proportional to its cross-sectional area. The effect is greatest in people with dilated deep veins, demonstrable radiologically.[3] This observation is the basis of a method now under trial to reduce the incidence of pulmonary embolism in hospital patients resting in bed. In 5426 general medical and surgical patients Wilkins and colleagues[4] have fitted every other case with knee-length elastic stockings, maintaining a pressure of 10–15 mm. Hg, and the controls with loose stockinet, only patients with cardiac œdema or obliterative vascular disease of the legs being excluded. There have been fewer pulmonary emboli among the patients wearing stockings, but the figures are not statistically impressive, chiefly because of the rarity of thrombo-embolism in general hospital patients unless they have congestive heart-failure. In further trials patients in congestive failure are to be included. If the results are convincing, elastic stockings may become the routine wear for hospital inpatients, especially those in whom the chance of thrombosis is highest—the elderly, the cases of congestive failure, and the patients recovering from major abdominal operations, particularly for neoplastic disease.

Another possible factor is suggested by Crane's[1] discussion of the predisposing causes of "effort" thromboses. The high intra-abdominal pressures produced by straining or lifting are conveyed down the veins of the leg if their valves are ineffective; and a vein may burst and thrombose at some weak spot, or where it is compressed by muscle or tendon or bent at a sharp angle, as may easily happen in the popliteal space. But if increased intra-abdominal pressure is a possible cause of thrombosis in the calf, may not postoperative clotting be favoured by the tight many-tailed bandages that many surgeons apply in their routine after-treatment?

Sir RUSSELL BRAIN, F.R.C.P., has been appointed an additional member of the Royal Commission on Marriage and Divorce.

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[1] Crane, C. *New Engl. J. Med.* 1952, 246, 529.

[2] Naide, M. *J. Amer. med. Ass.* 1952, 148, 1202.

[3] Stanton, J. R., Freis, E. D., Wilkins, R. W. *J. clin. Invest.* 1949, 28, 553.

[4] Wilkins, R. W., Mixter, G., Stanton, J. R., Litter, J. *New Engl. J. Med.* 1952, 246, 360.

Special Articles

SENIOR REGISTRARS

The Joint Consultants Committee has continued to represent to the Ministry of Health the importance of taking all practicable measures to minimise the hardship caused to senior registrars by the reduction in hospital establishments. The following statement has now been received by the committee from the chief medical officer of the Ministry.

Over recent years a good deal has, of course, been done to absorb a very large proportion of the large number of senior registrars who have been moving up the training ladder. There has been a considerable expansion in the consultant service; something like 400 new consultant posts were created in 1950 and over 200 more in 1951, apart from the considerable number of additional appointments made in the first eighteen months of the Service. It has, therefore, been possible to absorb many more people than could, in times of normal expansion, expect to get appointments.

More recently, as you know, we have—following a Whitley agreement—encouraged Boards to apply pretty strictly a policy of retirement of consultants at the age of 65, largely with the object of facilitating the absorption of more people who have finished their consultant training.

Furthermore, we have made it clear that the agreed overall training establishment of 960 senior registrars is not to be applied entirely rigidly, particularly in this transitional period. In particular, we have made it clear that in the four regional specialties—neurosurgery, plastic surgery, thoracic surgery, and radiotherapy—we should expect the existing establishment to be allowed to run down naturally to the new figure (though in other specialties we expect Boards to get down to the new establishment as soon as possible); that people who have completed their four years' training may in appropriate cases be allowed to take a fifth year in some other highly specialised branch of work where the training might be of particular value (e.g., a man who has completed training in general surgery might seek a fifth year appointment in vascular surgery or rectal surgery, and a man who has completed his training in orthopædic work might do an extra year in plastic surgery); and that Boards may also, if they are satisfied that this is essential for the efficient running of a hospital, keep on temporarily for up to a year after the end of his current year of appointment a senior registrar who is displaced from the training establishment.

These arrangements will serve to swell, particularly during this transitional period, the agreed number of 960 senior registrars and we do not think it would be reasonable to prolong the period of transition by announcing any further relaxations.

We are particularly concerned that the younger men who are now moving forward towards consultant status should not find their way blocked by the retention for an undue time of too many of the senior people who will, under the existing arrangements, have to be displaced.

We are also very anxious to avoid raising once more false hopes by prolonging the service of many people who cannot have any real chance of achieving consultant rank. I know that you made the point that we could make it perfectly clear to these people that we could hold out no promise of consultant status; but the mere fact of permitting people to stay on would in itself inevitably encourage them to hope. It is in our view best for these people who will be displaced to make up their minds now where, outside the hospital service, they are going to seek their permanent careers. Apart from the opportunities in the Services and the Colonies which we briefly mentioned, and in other smaller fields, like industry, I imagine that most of the people will want to settle down in general practice. Those who wish to succeed to a vacancy resulting from a death or retirement will have to stand their chance in competition with others; but there are still many areas which, in the opinion of the Medical Practices Committee, are not adequately doctored and in which there is no doubt room for more doctors, working either independently or in partnership. As you know, a Working Party is considering a new scheme for distribution of the Central Pool, following the Danckwerts Award. If the new scheme is favourable to the new entrant to general practice, that effect should become apparent towards the end of this year. Those who do undertake general practice may also be helped if the idea of general-practitioner clinical assistantships finds favour on an extended scale; this is one of the matters, of course, which we are still discussing in our review of the problems of junior medical staffing of hospitals.

I hope that this short statement will help the Joint Committee to understand what has already been done in an effort to help with the difficult senior registrar problem and what are the reasons for our present attitude.

CANCER NURSED AT HOME

CANCER is commonly dreaded as a painful and incurable illness, though in many cases it is neither of these things. Much stronger reasons for dreading it appear, however, in the report, just published, by the Joint National Cancer Survey Committee of the Marie Curie Memorial and the Queen's Institute of District Nursing, of their national survey[1] of patients with cancer nursed at home. Since cancer is commonly a disease of old people, it often falls out that there are few contemporaries in the family to look after the sick person, and there may be no younger members either. The disease is such that it often throws a heavy burden, especially of laundry work and night nursing, on the attendants, and there may be only neighbours to give such service. The result is that many old people with cancer end their lives in great loneliness, misery, and squalor.

The inquiry was carried out by district nurses; and after a pilot survey of 211 patients distributed in Bedfordshire, Buckinghamshire, Cardiff, Leeds, Norwich, and Worcester, 7050 patients throughout the United Kingdom were interrogated by the district nurses attending them, and questionaries filled in. More than two-thirds of the patients were 60 or over, and a quarter were over 75, but there was a baby of 4 months in the list as well as several people over 90.

The kind of situation in which some patients were existing is illustrated by case-histories such as the following:

> A totally blind woman of 85 was entirely dependent on her neighbours; her doctor was not able to get her a hospital bed, though she was critically ill. A woman of 76 was looked after by a sister of 88. Another woman, of 75, lived alone in a bed-sitting room, was seldom visited by her married children, and relied for care on the neighbours; the nurse thought she was not getting enough to eat.

Nearly two-thirds of the patients were women, but it is likely that many men patients were being nursed by their wives, and—since they did not call on the services of the district nurse—were not included in the survey. Most of the patients were looked after by relatives, the responsibility of running the home often being shared between two or more people; and the nurses found that relatives with good will for the work would contrive to make patients as comfortable as possible, in spite of difficulties and lack of amenities.

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[1] Published by the Marie Curie Memorial, 1952. To be had from 124, Sloane Street, London, S.W.1, or 13, Eglinton Crescent, Edinburgh, 12. Pp. 51. 2s. 6d.

Thus two daughters, who worked in a town some distance away, shared the night nursing of their father, dying slowly of carcinoma, and their mother, bedridden with leukæmia, and ran the home with the aid of a home help.

There were other cases, however, where relatives were unable or unwilling to reorganise their lives:

> One woman of 61, living with her husband and daughter-in-law who were both at work all day, got no food between breakfast and 6.30 P.M. The obstructive husband of another woman of 86 could only be prevailed on with difficulty to let the nurse wash her, though she was pitiably neglected.

Home helps have proved extremely valuable to those living alone. Nearly all the patients were being attended by their doctors. It was often clear that the patient had delayed before seeking advice: "Afraid to see a doctor" was a phrase used several times. At least one patient changed her attitude when the nurse explained that cancer is often curable.

Doctors did much to alleviate pain in these patients, and to relieve their mental distress; but one medical officer of health wrote:

> "My nurses all agree . . . that many patients suffer much unnecessary pain, and are inadequately sedated. They attribute this largely to the patients not telling the general practitioners about their pain."

There was no case of this reported in the survey, however; and probably most general practitioners would feel they hardly needed telling. The suffering of these patients was often enhanced by mental pain and fear; they were often distressed, too, because they were getting no treatment. Their spirits, at least, benefited when something was being done for them, even to the very end.

Nearly half of the 1832 patients who had had operations such as colostomy, jejunostomy, gastrostomy, tracheotomy, or cystotomy, were unable to attend to themselves without help; and the committee comment that patients should be taught to manage their apparatus before leaving hospital. Nursing equipment always seems to have been readily available from the local authority, the district nursing association, or the Red Cross. Some 43 people needed furniture, including single beds and night commodes; 380 needed sheets, blankets, or mattresses; and 180 needed day or night clothing. Some country dwellers suffered from lack of a water-supply or drainage system in their houses.

> In one particularly desperate case the patient, aged 67, lived with her crippled sister of 72 in a two-roomed cottage without drains or water. The patient, with multiple secondaries and infested with vermin, lay in the only bed, which her sister had previously shared with her. The sister now had to sit night and day on the clay floor of the living-room. They depended on neighbours for food.

Flat-dwellers sometimes had to share sink and lavatory with patients with advanced malignant disease. Cooking facilities were inadequate in the homes of 1 patient in 20, and many lacked any means of heating in the bedroom. Feeding varied with the attention given to the patient. Colostomy patients were found by one nurse to have a craving for bread-and-butter, and other members of the family often gave them their butter ration. About a third of the patients could get meals-on-wheels, and about one in five of these could have an invalid diet. The patient's laundry was done by relatives or friends in two-thirds of the cases, and by commercial laundries in another quarter. At least one patient used a municipal scheme for doing sick people's laundry, and about 1 patient in 20 did some or all of her own washing. But washing for cancer cases may be very unpleasant, and clearly some extension of municipal schemes is needed here.

The joint committee consider that many families looking after a patient at home suffer considerable hardship. They urge the need for residential homes taking not only cancer patients but others as well; patients could thus get skilled nursing without occupying hospital beds, and relatives would be spared much stress and mental suffering. Some old patients are very unwilling to leave their homes to go into an institution, but they might respond more readily to the idea of a residential home.

The committee find that patients need advice on the help they can get under the National Health Service Act, and from the National Assistance Board. Their families, too, need advice and encouragement; especially they need to be told that cancer is not, to the best of our knowledge, infectious. Voluntary bodies might well do much to help these patients, and voluntary or municipal schemes for providing attendance during the night are particularly needed; home-help services are invaluable and should be extended. A visiting occupational therapist or handicraft teacher could often get the patient to use his mind and hands, and so stop him brooding. The greatest material need, for many patients, is an adequate supply of bedding.

This report opens a door on some very dark scenes. Cancer is not the only disease by which the old and infirm are destroyed, nor the only one in which the growing enfeeblement of an elderly sufferer can lead to death in squalor. Schemes for the relief of cancer patients should take into account other sick people nursed at home by old and failing mates or companions. Such schemes are badly needed.

OPHTHALMOLOGICAL SOCIETY CONGRESS

THE 72nd annual congress of the Ophthalmological Society of the United Kingdom was held in Dublin on April 17–19, under the presidency of Mr. MAURICE WHITING. About 125 members were present, including several from the Continent and the U.S.A.

COLLAGEN DISEASES

In his Montgomery lecture Prof. DERRICK VAIL (Chicago) discussed the ocular complications of the diffuse collagen diseases. He suggested a classification which related the varied ocular manifestations to the systemic changes.

CORTISONE AND A.C.T.H.

Prof. ALAN WOODS (Baltimore) spoke about the therapeutic scope of cortisone and A.C.T.H. in ophthalmology, their proper dosage and method of administration, the range of their effects, and the mechanism of their action. He concluded that they had a definite but limited rôle, and that their benefits were restricted to the control of inflammation and exudation. The use of cortisone, and probably A.C.T.H., was contra-indicated in any form of ocular tuberculosis, and the drugs should be used with caution in chronic granulomatous infections. Dr. F. S. LAVERY compared the effects of cortisone when administered systemically in various eye diseases. Mr. E. G. MACKIE described the introduction of A.C.T.H. and cortisone therapy into the technique of an ophthalmological department, and discussed the methods of selecting cases, and the administrative problems that are raised.

SOME OTHER TOPICS

Mr. T. ROCHE reported that he had found no evidence of retrolental fibroplasia in Dublin.

Dr. ALAN MOONEY showed some examples of angiography in ocular disease.

LONDON TEACHING HOSPITALS

THE Minister of Health has made the following appointments, to fill vacancies caused by the retirement f a third of the members, to the boards of governors f the twenty-six London teaching hospitals. Of the 18 appointments, 164 are reappointments of retiring members. The names of medical members are shown in old type. Those now appointed will hold office until March 31, 1955.

ROYAL HOSPITAL OF ST. BARTHOLOMEW

Reappointed : **F. C. W. Capps,** F.R.C.S. ; Prof. **R. V. Christie,** F.R.C.P. ; Sir **James Paterson Ross,** K.C.V.O., F.R.C.S. : Sir Denys Lowson, Bt. ; A. M. Nelson-Barrett, J.P.

New members : Rear-Admiral P. K. Kekewich, C.B. ; Sir Frederick Tidbury-Beer. Two appointments outstanding.

LONDON HOSPITAL

Reappointed : Hubert Ashton, M.C., M.P. ; Mrs. I. M. Bolton ; **A. E. Clark-Kennedy,** F.R.C.P. ; Eustace Hoare ; Prof. **Clifford Wilson,** F.R.C.P. : B. A. Salmon ; **Stanley Thomas,** M.R.C.S., J.P.

New members : **Vernon C. Thompson,** F.R.C.S. ; Air Commandant Dame Felicity Hanbury ; Professor **Victor Dix,** F.R.C.S., and H. R. Moore (until March 31, 1954).

ROYAL FREE HOSPITAL

Reappointed : **G. E. Breen,** O.B.E., M.D. ; Alderman Mrs. Ruth Carnegie ; Ernest Green, C.B.E., M.A., J.P. ; the Hon. Mrs. J. Mulholland ; the Hon. P. M. Samuel, M.C.

New members : Miss **Geraldine Barry,** F.R.C.S. ; **D. H. Geffen,** M.D. ; **J. C. R. Hindenach,** F.R.C.S. ; H. J. Treby.

UNIVERSITY COLLEGE HOSPITAL

Reappointed : the Hon. Margaret Bigge ; **C. W. Flemming,** O.B.E., F.R.C.S. ; **K. E. Harris,** F.R.C.P. ; **J. C. Hawksley,** C.B.E., F.R.C.P. ; **S. Cochrane Shanks,** F.R.C.P., F.F.R. ; H. W. K. Wontner.

New members : Captain the Hon. R. M. Greville ; G. R. Holman ; L. Moss.

MIDDLESEX HOSPITAL

Reappointed : Sir **Harold Boldero,** F.R.C.P. ; F. H. Doran ; W. K. Fitch ; F. J. B. Gardner, M.C. ; J .H. Hambro, C.M.G. ; Lord Latymer ; Henry Lesser, C.B.E., LL.B. ; E. C. Tyler.

New members : Sir **Harold Graham-Hodgson,** K.C.V.O., F.R.C.P., F.F.R. ; J. C. Maude, Q.C. (until March 31, 1953).

CHARING CROSS HOSPITAL

Reappointed : **R. A. Hickling,** F.R.C.P. ; H. J. Wasbrough ; Prof. **H. W. C. Vines,** M.D. ; G. W. Ganter ; V. F. Decks ; Alderman B. Lewis ; **N. C. Lake,** F.R.C.S.

New members : Mrs. M. R. Forbes, J.P. ; T. Banks.

ST. GEORGE'S HOSPITAL

Chairman : Sir Malcolm Trustram Eve, Bt., C.B.E., M.C., Q.C. (until March 31, 1954).

Reappointed : the Hon. Terence Eden, M.C. ; Sir **Claude** [illegible] S. ; **Hugh Gainsborough,** F.R.C.P. ; [illegible] ; W. E. Meade ; **D. Stark Murray,** [illegible], D.S.O., M.C. ; Alderman Mrs. M. Walkden, J.P.

New members : **M. I. A. Hunter,** F.R.C.P. ; the Hon. Lady Monckton, C.B.E. (until March 31, 1954) ; the Rt. Hon. Sir Frank Soskice, Q.C., M.P., and Brigadier H. L. Roy Matthews, C.B.E. (until March 31, 1953).

WESTMINSTER HOSPITAL

Reappointed : H. M. Clowes, D.S.O. ; Sir Louis Greig, K.B.E., C.V.O. ; H. P. R. Hoare ; Lord Kershaw ; **W. Ernest Lloyd,** F.R.C.P. ; Group-Captain C. A. B. Wolcock, O.B.E., A.F.C. ; F. A. Yarrow ; Alderman the Rev. Harcourt Samuel.

New members : The Hon. Mrs. Bernard Waley Cohen, M.A., J.P. ; **F. Dudley Hart,** F.R.C.P. ; the Hon. Mrs. Asheton (until March 31, 1953) ; Sir Austin Hudson, Bt., M.P. (until March 31, 1954).

ST. MARY'S HOSPITAL

Reappointed : Lord Cohen ; **Joel Green,** L.R.C.P.I. ; E. E. Lawley ; F. Lawrence, J.P. ; Mrs. Jane Lesser ; H. N. Sporborg, C.M.G. ; L. D. Thomson.

New members : M. W. Lloyd Owen ; **A. C. Palmer,** O.B.E., F.R.C.O.G.

GUY'S HOSPITAL

Reappointed : **E. R. Boland,** C.B.E., F.R.C.P. ; C. A. Chadwyck-Healey, O.B.E. ; Sir **John Conybeare,** K.B.E., M.C., F.R.C.P. ; Miss D. E. Dovell ; R. A. Hayward ; A. B. Kennedy, J.P. ; **A. Talbot Rogers,** M.B. ; **E. G. Slesinger,** O.B.E., F.R.C.S.

New member : Squadron-Leader F. H. Bowyer, M.B.E., J.P.

KING'S COLLEGE HOSPITAL

Reappointed : M. V. Courage ; Sir **William Gilliatt,** K.C.V.O., F.R.C.O.G. ; **V. F. Hall,** M.R.C.S., F.F.A. R.C.S. ; R. A. Hornby ; **J. H. Peel,** F.R.C.O.G. ; J. T. Pyne.

New members : **F. S. Cooksey,** O.B.E., M.D. ; Mrs. Margaret Purkis ; Squadron-Leader G. Edgar. One appointment outstanding.

ST. THOMAS'S HOSPITAL

Reappointed : Prof. **W. G. Barnard,** F.R.C.P. ; **J. St. C. Elkington,** F.R.C.P. ; A. G. Linfield, O.B.E., J.P. ; Lindsay Mackie, B.A. ; Prof. **George Perkins,** F.R.C.S. ; **J. Forest Smith,** F.R.C.P. ; **C. H. Vernon,** M.B. ; A. H. Winterbotham.

New member : F. A. K. Betty.

HAMMERSMITH, WEST LONDON, AND ST. MARK'S HOSPITALS

Reappointed : R. P. Chambers ; the Hon. John Fremantle ; Mrs. E. Hailstone, J.P. ; Mrs. Myrtle Lane ; Prof. **John McMichael,** F.R.C.P. : **C. E. Newman,** F.R.C.P. ; **Maurice Shaw,** F.R.C.P. ; Prof. R. M. Titmuss.

New members : J. G. Gapp ; **Ronald Cove-Smith,** M.R.C.P. (until March 31, 1954).

THE HOSPITAL FOR SICK CHILDREN

Reappointed : Lady Ashley Cooper ; **James Crooks,** F.R.C.S. ; L. Farrer-Brown, M.A., J.P. ; C. A. Lucas ; **Wilfrid Sheldon,** F.R.C.P.

New members : **A. P. Norman,** M.R.C.P. ; A. Sumption ; S. Dane.

NATIONAL HOSPITALS FOR NERVOUS DISEASES

Reappointed : Miss K. Cooper-Abbs ; R. Blundell ; E. Cuddon ; **F. M. R. Walshe,** O.B.E., M.D., F.R.S.

New members : Prof. **A. J. Lewis,** F.R.C.P. ; **J. B. S. Lewis,** M.D. ; **Douglas McAlpine,** F.R.C.P.

ROYAL NATIONAL THROAT, NOSE AND EAR HOSPITAL

Reappointed : **C. Gill-Carey,** F.R.C.S. ; **Adam Gray,** M.D. ; F. N. Hornsby ; Miss Rosalie Drayer, S.R.N., S.C.M. ; Mrs. O. A. MacIver ; Mrs. F. Timpson ; Mrs. C. Turquet.

New member : **Anthony Radcliffe,** F.R.C.S.

MOORFIELDS, WESTMINSTER AND CENTRAL EYE HOSPITAL

Reappointed : Jonathan Backhouse ; **R. C. Davenport,** F.R.C.S. ; Sir **Stewart Duke-Elder,** K.C.V.O., F.R.C.S. ; the Hon. Arthur Gore ; F. W. Lascelles, C.B., M.C. ; **T. Keith Lyle,** C.B.E., F.R.C.S. ; Alderman Charles H. Simmons, J.P.

BETHLEM ROYAL AND THE MAUDSLEY HOSPITAL

Chairman : Mrs. M. Ormerod, B.A.

Reappointed : Prof. **F. R. Winton,** M.D. ; Tom Brown, M.COM., F.I.I.A., J.P. ; Sir **Allen Daley,** F.R.C.P. ; **W. G. Masefield,** M.R.C.S., D.P.M., J.P. ; **Doris Odlum,** M.R.C.S., D.P.M.

New members : **D. L. Davies,** D.M. ; **Janet Day,** M.B., J.P. ; **Arthur Harris,** M.D.

ST. JOHN'S HOSPITAL FOR DISEASES OF THE SKIN

Reappointed : Mrs. D. E. Clark ; **R. M. B. MacKenna,** F.R.C.P. ; A. H. Montgomery ; **J. E. M. Wigley,** F.R.C.P. ; E. Snowdon, J.P.

New member : **R. T. Brain,** F.R.C.P. (until March 31, 1954).

HOSPITAL FOR DISEASES OF THE CHEST

Chairman : Widdrington Stafford.

Reappointed : the Hon. Mrs. Nigel Birch, O.B.E.; L. B. Prince; Mrs. K. E. Rae; **J. G. Scadding**, F.R.C.P.; **J. Smart**, M.R.C.P.; Sir **Clement Price Thomas**, K.C.V.O., F.R.C.S.

New member : W. J. Carter. One appointment outstanding.

ROYAL NATIONAL ORTHOPÆDIC HOSPITAL

Reappointed : **H. J. Burrows**, F.R.C.S.; Brigadier Ralph Micklem, C.M.G., C.B.E.; Harold Sutcliffe, M.P.; Lady Wakehurst.

New members : **V. H. Ellis**, F.R.C.S.; Colonel R. R. Hoare, D.S.O., M.C.

NATIONAL HEART HOSPITAL

Reappointed : Lady Kythe Hendy; **G. A. Jennings**, F.R.C.P.; Mrs. J. R. Keen; Sir William Arbuthnot Lane, Bt.; **Paul Wood**, F.R.C.P.

New member : **Graham Hayward**, F.R.C.P.

ST. PETER'S AND ST. PAUL'S HOSPITAL

Reappointed : Vice-Admiral J. W. Durnford, C.B., R.N. retd; A. R. G. Hudson, O.B.E.; **A. C. Morson**, O.B.E., F.R.C.S.; E. D. J. Matthews, O.B.E., F.R.I.B.A.; **J. G. Sandrey**, F.R.C.S.; Miss Rosina Whyatt.

New members : **H. H. D. Sutherland**, M.R.C.S.; A. Sherriff (until March 31, 1954).

ROYAL CANCER HOSPITAL

Reappointed : Lord Ashcombe; G. Koch de Gooreynd, O.B.E.; Mrs. Murray Graham; Prof. **Alexander Haddow**, M.D.; S. L. Lyons; Prof. **D. W. Smithers**, F.R.C.P.

New member : Sir **Stanford Cade**, K.B.E., C.B., F.R.C.S.

QUEEN CHARLOTTE'S AND CHELSEA HOSPITALS

Reappointed : **A. C. H. Bell**, F.R.C.O.G.; Alderman Mrs. O. A. F. Davies; A. J. Espley, C.B.E.; **Charles Read**, F.R.C.O.G.; J. H. Senior; Alderman R. G. Wharam; C. L. Woolveridge.

New member : **W. R. Winterton**, F.R.C.O.G. (until March 31, 1954).

EASTMAN DENTAL HOSPITAL

Reappointed : F. J. Ballard; Mrs. D. Holman; A. D. Page; **F. C. Wilkinson**, M.D., F.D.S. R.C.S.

New member : **W. G. Cross**, M.S., L.D.S. R.C.S.

Medicine and the Law

Surgeon's Successful Claim

IN a recent case at the Burnley county court,[1] where a consultant surgeon successfully sued for a fee of 50 guineas, the patient and her husband pleaded as a defence that they had been treated under the National Health Service.

The surgeon stated that he was called in at 11.15 P.M. and diagnosed a perforated ulcer. The patient was desperately ill, with signs of general peritonitis, and an immediate operation was essential. She said she must be treated as a private case; he obtained a private room in a hospital, and the operation was performed at once; it had been agreed that a consultant anæsthetist should be engaged; the husband said "nothing but the best for my wife." Her medical attendant testified that the patient herself had named the surgeon, whereupon he had told her that, if she wanted a particular surgeon, she would have to pay for him.

The witness was cross-examined in the attempt to show that he had failed to discharge a statutory duty in that he had not informed the patient of her position under the National Health Service Act, but the judge intervened with the comment that it would be an intolerable imposition on the medical profession if they had to explain their rights under the Act to every patient.

The defendants, the patient and her husband, denied the conversations which would have established their liability. The judge, however, did not accept their evidence; he refused to assume that "a surgeon of high standing and his fellow doctor had come to the court and told a pack of lies." He could not believe that their evidence was fabricated. Judgment was given for the surgeon for his fee of 50 guineas and for the anæsthetist's fee of 7 guineas.

The McNaughten Rules Again

The appeal against a conviction for murder in the case of R. *v.* Windle[1] raised three points of interest. First, the Court of Criminal Appeal, in reaffirming the Rules in McNaughten's case, added a sort of expository footnote. Secondly, although the conduct of the accused had been unquestionably abnormal, the trial judge took the bold course of declining to leave the issue of insanity to the jury. Thirdly, the court heard mention, perhaps for the first time in the judicial experience of its members, of the possibility of "communicated insanity."

The facts were as follows. The accused, a small man of scant resolution and weak character, was unhappily married to a woman 18 years his senior. Doctors might have deemed her certifiable; she was constantly talking of committing suicide. Her husband, obsessed with this, talked as constantly of it to his fellow-workmen till they were sick and tired of hearing of it. One day one of them, whether seriously or not, said "Why not give her a couple of dozen aspirins?" The husband did in fact give her 100 aspirin tablets, with fatal results. He sent for a doctor and later told the police what he had done, adding "I suppose I shall be hanged for that." His defence at the trial was insanity. A doctor was called for the defence. It was said that the conditions of "communicated insanity" were present—the strong character, already insane, "communicating" disease of the mind to the weak character. The prosecution called rebutting evidence from another doctor. The trial judge held that there had been no evidence of such insanity as would in law amount to irresponsibility and justify the defence. He ruled that there was no issue of insanity to leave to the jury. The Court of Criminal Appeal says this was a strong line to take but it was one which a trial judge might, and indeed ought to, take if convinced that there was no evidence on the particular issue.

The case therefore brought the court back to the McNaughten Rules. These are, first, that the jury ought to be told that every person is presumed to be sane, and secondly that, to establish a defence of insanity, the accused must clearly prove that, at the time of committing the act, he was "labouring under such defect of reason, from disease of the mind, that he did not know the nature and quality of the act which he was doing, or, if he did know it, did not know he was doing what was wrong." It was that last word which was found to need explanation. Both the doctors at the trial agreed that Windle knew perfectly well that he was doing what the law forbade. But might he not, argued the defence, have thought, in the misery of his life with a nagging and tiresome wife who continually talked of suicide, that it might be better and kinder to put her out of her suffering? Might he not have thought it beneficial and excusable and so not "wrong"?

The Court of Criminal Appeal made it clear that "wrong" in the McNaughten Rules means forbidden by law; it does not mean morally unjustifiable. Courts of law, said the Lord Chief Justice, "can only distinguish between that which is in accordance with the law and that which is contrary to it. The law cannot embark on an inquiry whether an act is morally right or wrong."

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[1] *Northern Daily Telegraph*, May 2.

[1] *Times*, May 13.

dictum might in other legal contexts be open to ument, but the result for Windle was inevitable. knew that he had done something against the law, d he realised what punishment the law provided for rder. His appeal was consequently dismissed, though doubt, as Lord Goddard observed, his case will receive nsideration elsewhere.

The Unaccountable Swab

At a recent inquest at Sutton[1] there was evidence at a patient died in hospital three days after an opera- and that a cotton-wool swab 1 × $^5/_8$ in. was und in the bronchus. The evidence of the pathologist s that this object must have been introduced during e; he thought it had been in the bronchus two or ree days; a swab of this size was sufficient to have ocked the bronchus completely. The anæsthetist d the sister present in the operating-theatre stated at no such cotton-wool swab was used at the operation. appeared that cotton-wool had been used in the ward r cleaning the patient's face and mouth after the eration, but the nurses concerned stated that none of eir swabs was missing.

The patient's pulse collapsed immediately after the peration, and the heart stopped for some four minutes; rtificial respiration was started and continued until reathing became spontaneous. During the following ight there were choking fits. The patient's condition was nsistent with the collapse of the right lower lobe of the ng. The coroner observed that he had been unable o elicit any evidence of how exactly this swab arrived here it did. He was satisfied that it was introduced nto the man's body while he was under treatment in ospital, and its presence in the bronchus was responsible or his death. A verdict of death by misadventure was ecorded.

Parliament

Corneal Grafting Bill

In the House of Commons on May 14, Mr. GERALD WILLIAMS was granted leave to introduce a Bill to make rovision for the use of eyes of deceased persons for herapeutic purposes.[2]

QUESTION TIME

General-practitioner Hospitals

Mr. READER HARRIS asked the Minister how many general-practitioner hospitals existed on July 5, 1948; how many of these still existed as general-practitioner hospitals; and to what uses the others had been converted.—Mr. IAIN MACLEOD replied: There were 386 general-practitioner hospitals (excluding maternity homes) on July 5, 1948. Of these 351 still exist as general-practitioner hospitals; 21 have become general hospitals; 6 annexes of general hospitals, 5 special hospitals, 3 general-practitioner maternity homes. A number of additional general-practitioner units have been provided elsewhere.

General Dental Service for Children

Mr. JOHN MORRISON asked the Minister of Health the number of children given treatment in the general dental service.—Mr. MACLEOD replied: It is estimated that in the four months to Dec. 31, 1951, 330,000 children were given treatment, other than emergency treatment, in the general dental service.

Psychiatric Treatment of Children in Scotland

Major NIALL MACPHERSON asked the Secretary of State for Scotland how many child psychiatrist consultants were employed by each regional hospital board in Scotland.—Commander T. D. GALBRAITH replied: Psychiatric treatment of children is normally provided as part of the general psychiatric service. The South Eastern Regional Hospital Board, however, have one consultant whose duties are restricted to psychiatric work with children.

Colonial Nurses and Doctors

In answer to a question Mr. OLIVER LYTTELTON, Secretary of State for the Colonies, stated that approximately 260 doctors and 40 nurses from Colonial territories had completed their training in this country since the war and had returned to work in their own areas.

Psychiatric Treatment for Prisoners

Replying in the House of Lords on May 13 to Earl Howe, LORD SIMONDS, the Lord Chancellor, said that a protracted search had been made on behalf of the Prison Commissioners for a suitable site on which to erect an institution as recommended in the report of Sir Norwood East, who is medical commissioner of prisons, and the late Dr. Hubert on The Psychological Treatment of Crime, for the care, study, and treatment of selected groups of prisoners of carefully defined classes, most of whom would require active psychiatric treatment. The institution would be within the prison system and under the control of the Prison Commissioners. It would have no connection with Broadmoor Institution, and persons who had been found insane would not be eligible for admission. A site at the disposal of the Crown near Merstham, in Surrey, within the Green Belt area, had now been brought to the notice of the commissioners, who were in consultation with the Minister of Housing and Local Government about it.

Doctors' Lists

Mr. SOMERVILLE HASTINGS asked the Minister of Health the numbers of general medical practitioners in the National Health Service who had under 1000, 1000–1500, 1500–2000, 2000–3000, and over 3000 patients on their lists; and the numbers in each of these groups who had additional patients on their lists in respect of assistants employed by them.—Mr. MACLEOD replied: At January 1, 1950, the numbers (excluding limited lists) were as follows:

Patients	*Doctors*
Under 1000	2400
1000–1500	1613
1500–2000	1936
2000–3000	4059
Over 3000	5916

The information asked for in the second part of the question is not available.

N.H.S. Unestablished Doctors

In answer to a question Mr. MACLEOD stated that the numbers of assistants employed by general medical practitioners in the National Health Service at March 31, 1950, and at the end of 1951, were 2088 and 1998, respectively.

General Practice Trainees

In answer to a question Mr. MACLEOD stated that the numbers of trainee assistants employed in general medical practice at March 31, 1949, 1950, and 1951 were 119, 303, and 359 respectively.

Charges for Certificates

In answer to a question Mr. MACLEOD stated that general practitioners were required to provide free of charge to their National Health Service patients any medical certificate included in the list forming the second schedule to the National Health Service (General Medical and Pharmaceutical Services) Amendment (No. 2) Regulations, 1949. This list included certificates required for claims to sickness benefit under the National Insurance Act, but not those requested by friendly societies or sick clubs for which a doctor may charge if he wishes.

Hospital Costs

Mr. J. G. MORRISON asked the Minister why the salaries and wages of other staff made a greater addition to the national average cost of maintaining a patient in a general hospital than the salaries and wages of the medical or of the nursing staff, respectively.—Mr. MACLEOD replied: "Other staff" covers a large variety of grades, such as staff engaged on the maintenance of plant and buildings, laundries, farms and gardens, administrative, clerical, professional and technical staff, ward orderlies and ward maids, kitchen staff and porters. The total of the salaries and wages paid to them is greater than the total salaries paid to either doctors or nurses.

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1. *Wimbledon Borough News*, May 9.
2. See *Lancet*, March 8, 1952, p. 500.

In England Now

A Running Commentary by Peripatetic Correspondents

ASSISTANT WITH A VIEW

My present abode is a flat near the surgery:
The rent and the stairs are confoundedly steep;
The agent who let it committed flat perjury—
But at least it is somewhere to sleep.

The flat (more correctly described as an attic)
Has taps, pipes, and cistern all leaking like fun;
The prospect is bleak, the prognosis rheumatic,
But the lease has a long time to run.

The daily is willing but thinks I like porridge;
When told that I don't she's astonished; the nymph
In this matter of porridge is firm and incorrig-
ible, so it's porridge *ad inf.*

The diet is dismal: for dinner I'm cheered with
A surfeit of beans on a piece of wet toast;
The sweet is a shape, but amorphous and smeared with
A sliver of jam at the most.

The elderly ball-tap's producing a keening
And making me jump with its spine-chilling clank;
Attempts at inspection result in my beaning
Myself on the galvanised tank.

I'm itching to switch to some clublet or publet:
My present surroundings are driving me mad;
But the lease and the landlord forbid me to sublet—
I've had it, and have I been had!

* * *

The most striking characteristics of the doctors depicted in Hollywood films are the unorthodoxy of their diagnoses and their reckless disregard of accepted surgical techniques, leading nevertheless to astounding therapeutic successes.

*At the end of his heart-rending interview with the girl's tearful relatives the surgeon, ready clad in sterile gown and gloves, shakes hands all round, turns on his heel with an upward glance of infinite sadness, and deftly whips the villain's bullet from the heroine's heart. He does not need to wash his gloved hands or (in period pieces) dip them into the bowl of carbolic provided—*his* incisions *never* go septic. We can be sure that the heroine will recover in half an hour and that love will shield her from all complications.

In a contemporary transatlantic journal, the Motion Picture Association of America have published an analysis of the parts played by doctors in American films. They tell us that in 1949 doctors were portrayed 211 times in 411 films and by 1950 the totals had risen to 237 portrayals in 428 films. In 1949 they were assigned parts as villains 12 times, but only 3 films made them obviously villainous; in the other 9 they were only moderately so. The figures for 1950 were much the same; 3 obvious rogues and 10 not so obvious ones. The report is careful to point out that "This does not necessarily mean that the portrayal showed doctors as guilty of malpractice or unethical conduct; they may simply have been the father of the heroine, blocking access to the lover in some unreasonable manner." That is a relief anyway! And since only 5·5–5·7% of the doctors were bad hats it is not surprising that they were *never* portrayed unsympathetically *as a group;* their cloth was respected as the following figures show.

Year	*Sympathetic and prominent*	*Sympathetic but less prominent*	*Sympathetic as a group*
1949	22 ..	128 ..	3
1950	21 ..	112 ..	4

We may safely deduce that the 7 characters grudgingly portrayed sympathetically *as a group* included the 6 obvious villains already enumerated as individuals—many of them hideous inhuman brutes blocking access to the heroine; keeping the hero at bay with their scalpels, patella hammers, and obstetrical forceps while their terrified and trembling daughters are shut up in the ice-box to cool their passion. The monsters! Nevertheless, their stethoscopes swing proudly from their necks; and they wield their knives (and probably their forceps, offstage) neatly and efficiently, a credit to the profession *as a group.*

Ever since my student days, I have thought admiringly of the film-director's and film-actor's affluence and influence on other people's lives. In my dreams I produce immensely successful films, featuring melodramatic scenes freely adapted from the everyday experience of medical students and surgeons of my acquaintance. The humour is provided by real-life urologists and anæsthetists whose wit I have always appreciated. But the American report says it is not in the best of taste for a doctor to appear as a comic; in 1950 he was portrayed only twice in humorous rôles. However, some hope remains, for the M.P.A.A. remarks: "Evidently film makers have passed over some of the humour of a doctor's existence, and perhaps there is a clue in this for the alert scenario writer." A masterpiece of understatement, surely. Without overstepping the bounds of sympathy, and sticking as close to reality as libel laws allow, even a semiconscious scenario-writer ought to be able to depict us *as a group* or individually and leave the audience rolling about the floor holding their costal margins.

* * *

"Switchboard? the medical registrar doing his, please." . . . Brr-Brr . . . Brr-Brr . . . Brr—"That you Cedric? Wonder if you'd mind coming in to see a new case. A boy of 18 months. . . . Mother says he looks queer; he does too. . . . He's got marked hirsutes, with horny skin on his palms and soles; his head is odd too—right ear lower than the left. . . . Plagiocephaly, you say? . . . It could be. . . . He's got a fixed glassy stare, with widely dilated and immobile pupils. . . . Yes, he's always like that; but this morning, if you press on his tum he lets out a horrible bleating noise. . . . You'll come in? . . . His name?—Edward Bear. . . . You *won't* come? . . . And tell Teddy to what? . . ." *Click!*

He's mad that he didn't come now, for he missed the best pyknic syndrome we've ever had.

* * *

To take or not to take. That is the familiar question we all have to answer when packing. But when one is setting out on a foot safari it becomes far more pressing; and that is why I left my forceps behind.

We reached the out-station dispensary in the foothills of the Livingstones at 5.30 P.M., just as it was getting dark, and were met by the hospital dresser who asked us to see a girl in the village who had been in labour for 21 hours. The dresser himself had arrived at the dispensary only two days before, and a hurried search did not reveal either a Higginson or a catheter. We walked for twenty minutes, carrying our hurricane lamps, and then came on a small group of women sitting on the ground round a fire. Further on another group was sitting round another fire, and a few yards away from them the patient herself lay stark naked across the furrows of an old maize plantation, surrounded by yet more women, two of whom had their dirty hands in the girl's vagina. In accordance with village custom, the girl had been encouraged to bear down at each pain since labour began, and for all that time she had been allowed no food, drink, or rest. All the same, we hoped that a little nourishment and rest between pains would do the trick, and it did. The baby was delivered and the mother and child are doing well.

I still do not take my forceps on safari, but I am seriously thinking of incorporating a catheter in the lining of my topee.

* * *

News from School.—"Last week we went down to Messrs. X to learn about public and economic affairs. We were supposed to be going round the offices, but on the day they said we couldn't, so we went round the biscuit part and had biscuits. Another day we went to the milk pasteurising plant to see what it was like and to find its faults (that was Biology) and on Wednesday last we had the public analyst up in prep to talk about publically analysing."

Letters to the Editor

CROSS-MATCHING OF BLOOD

SIR,—Most workers agree that tile or slide techniques for grouping and cross-matching blood are not so reliable or sensitive as the tube technique—a view stated officially, for example by the Medical Research Council.[1]

Dr. Discombe (April 12) describes a slide technique of cross-matching blood in which a loopful of well-mixed donor's blood is mixed with a few drops of recipient's serum and, after a couple of minutes, the fibrin web is removed. When grouping or cross-matching blood, we consider it desirable to avoid clotting since the distinction between minute clots and agglutinates may be difficult. Moreover, clots are known to enmesh agglutinates which might be removed with the clot, so resulting in a false negative reading. Dr. Discombe goes on to say: "Cover with a coverslip, and examine for rouleaux or agglutination (×400); neglect pure rouleau formation, but, if [illegible] e present . . ." Our own experience, [illegible] sometimes it may be exceedingly difficult to distinguish between rouleaux and true agglutination when the red cells are suspended in viscous media. Sometimes, when harmful agglutinins—e.g., anti-Rh—are present, rouleaux may also form. Rouleaux, of course, can usually be obviated by diluting the recipient's serum 1 : 2 in saline and then repeating the cross-match test, but the ideal would be to apply the Coombs test. In the slide technique described by Dr. Discombe, the results are read in a few minutes. It is, however, well known that some harmful agglutinating antibodies may cause agglutination only after a long time—an hour or more.

The criterion of an effective cross-match test is not so much that it is successful in a large number of cases, as that it will detect harmful antibodies when these are present. Very rarely certain harmful antibodies—e.g., anti-S or Fy^a—may not agglutinate red cells with which they are incompatible, irrespective of the medium in which they are suspended, and such antibodies will then only be detected by the Coombs test. It is hardly to be expected that tests to recognise such harmful antibodies will be applied in most laboratories. In cross-matching blood it is very important to know the history of prospective recipients with regard to pregnancies or transfusions; and, if the history is suspicious, it may be essential to cross-match by a very sensitive technique such as titration (seven tubes) in albumin, or, better still, by the Coombs technique. If the recipient is known to have irregular antibodies, both these tests should be done. *In the description of any cross-matching technique this point should be made clear.* If the history is suspicious, then the compatibility tests are best performed by a laboratory equipped to cross-match blood by very sensitive techniques. Incidentally, in tests carried out in viscous fluids zoning may prove a difficulty, and, therefore, it is best to do the test with more than one dilution of the recipient's serum. In describing a cross-match test it is important to emphasise the need for adequate control tests along with the cross-match test.

Cardiff. R. DRUMMOND
Director, Regional Transfusion Service.

Manchester. F. STRATTON
Director, Regional Transfusion Service.

HICCUP DURING ANÆSTHESIA

SIR,—Your correspondents on this subject have directed attention mostly toward remedies. This is natural since hiccup is troublesome and must be remedied at once. It is nevertheless a useful sign. When it appears strongly in a patient in apnœa it shows two things: (1) that apnœa is due not to paralysis by the relaxant but to depression of the respiratory centre, usually by excessive artificial ventilation; and (2) that relaxation is inadequate.

The clear indication, therefore, and certain remedy is to give more relaxant. Either a paralysing dose of succinylcholine may be used and repeated as often as necessary; or, if there is yet some time to go before the operation will be completed, curare or 'Flaxedil' may be given in dose sufficient to reduce the hiccup to a negligible movement. In either case artificial respiration is continued, but to an extent which will redress the balance of carbon dioxide and avoid acapnia.

I have tried many of the remedies recommended but found no other one that is wholly reliable.

St. Thomas's Hospital,
London, S.E.1. J. G. BOURNE.

CAT-SCRATCH-FEVER

SIR,—Much interest in the disease known as cat-scratch fever has been aroused by recent annotations[1] and correspondence in your journal, and it is probable that further cases will come to light.

From the material sent to us from the case reported by Dr. Campbell and Dr. Wheaton in your issue of May 10, we have prepared an antigen suitable for a diagnostic intradermal test. The antigen is not standardised; and, owing to the absence of any suitable controls, it has not been possible to assess its activity or specificity. Only limited supplies are available, but we shall be pleased to send some for trial to practitioners having suspected cases under their care. Our knowledge of the disease is very incomplete; and we should, therefore, be grateful for material from fresh cases with which to carry out ætiological studies and to prepare fresh batches of antigen.

You have drawn attention to the association of pasteurella with wounds caused by cats. Several cases of infection with this organism have recently been recognised, and it is therefore desirable, before testing a patient with the cat-scratch-fever antigen, to exclude the presence of pasteurella or other pathogenic organisms.

Central Public Health Laboratory,
Colindale Avenue, London, N.W.9. H. J. BENSTED
Director of Laboratories.

FUNCTIONAL DISORDERS OF SMALL BOWEL AFTER GASTRECTOMY AND VAGOTOMY

SIR,—Dr. Glazebrook is to be complimented on his courageous and stimulating article (May 3).

In particular his comment anent the patient who complains after operation is most revealing. In our book[2] we expressed this same opinion from a different point of view, and one reviewer stated that we arrived at our conclusions without experimental work. Surely the experimental work is done for us, every time that a surgeon removes the bulk of a healthy stomach—in order to treat an ulcer in the duodenum, which is left intact with its ulcer. Is not the moral that gastrectomy (partial or subtotal) as a method of treatment of gastroduodenal ulceration is commonly worse than the initial disease?

We would make a very strong plea for reconsideration of the ætiology of gastroduodenal ulceration; and we feel that, even if the views we have put forward are not orthodox, at least they are worth considering if by studying our hypothesis some better assessment of the ulcer problem and its treatment can be arrived at.

We appeal for an open mind towards unorthodoxy in this field, when the results of orthodoxy are not only so barren but, as is seen from the cases studied by Dr. Glazebrook, actually maleficent.

DAVID HALER
London, W.1. KASPER BLOND.

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[1] Determination of Blood Groups. Medical Research Council War Memorandum, no. 9., H.M. Stationery Office, 1943.

[1] *Lancet*, Feb. 9, 1952, p. 302; *Ibid*, May 10, 1952, p. 958.
[2] Haler, D., Blond, K. The Liver. Bristol, 1950; chapter 7.

SICKLE-CELL ANOMALY IN GREECE

SIR,—The finding of an occasional sickle-cell-trait carrier in Greece is not surprising; but the observation by Dr. Caminopetros (April 5) of such a high incidence as 49·1% in Athens is almost sensational.

By the sickle-cell-trait phenomenon is meant the transformation of the normal red cell into sickle or holly-leaf shapes on deoxygenation; the cause is low solubility of reduced S hæmoglobin, which crystallises inside the cell.[1] It is not widely enough realised that all the bizarre forms noted in sickle-cell anæmia can be simulated by mixing the blood of a normal white man with glue or gelatin.[2] This reaction depends on two factors: (1) the mechanical process of the cells being mixed with a very viscous solution, and (2) the nature of the colloidal suspension. It can also be noted at times on the edge of a blood film of normal individuals when plasma dries slowly enough for the concentration to affect the red cells before they are dry. In contrast to the intrinsic change seen in "sicklæmia," the transformation caused by extrinsic factors cannot be reversed by oxygenation but can be reversed by the addition of small amounts of water.[2]

Before accepting the statement that many hundreds of thousands of Greeks are sickle-cell-trait carriers, and that all patients with Mediterranean anæmia are sicklæmics as well, one would be glad to have from Dr. Caminopetros reassurance on these points. Was the blood sealed under conditions where it had no contact with the sealing material? One drop of blood from each of 100 random Athenians might perhaps be mixed on a slide with a fresh 2% solution of sodium metabisulphite, covered with a coverslip, and looked at after 30 minutes. If sickle cells are then found the phenomenon will be comparable with that reported in American Negroes, Africans, and Indian Weddians.

St. Bartholomew's Hospital,
London, E.C.1.
H. LEHMANN.

*** Dr. Lehmann's letter has been shown to Dr. Caminopetros, whose reply follows.—ED. L.

SIR,—In my article I omitted a full description of the Scriver-Waugh and the Itano-Pauling methods, which I used to detect sickling, because they have become routine everyday methods.

A drop of blood, drawn from a finger which has been constricted by a rubber band for 5 minutes or more (up to an hour in most of my examinations) is sealed with 'Vaseline' between a coverslip and a slide. Under these conditions the red blood-cells undergo slow but progressive evolution to the elongated form with filamentous flagella at both ends; the transition takes 4–12 hours at a temperature of 36°C. This is the real sickle-cell phenomenon. Perr[3] insists that "the most reliable and the most practical method for the detection of the sickle-cell trait is the moist stasis method of Scriver and Waugh."[4]

The method of Itano and Pauling[5] is simpler, quicker, and equally reliable; but it is not so convenient for mass examinations outside the laboratory, because it is difficult to transport the preparations, which are not usually sealed with vaseline.

As far as I know, Dr. Lehmann is the first to doubt the accuracy of the Scriver-Waugh method when he says: "It is not widely enough realised that all the bizarre forms noted in sickle-cell anæmia can be simulated by mixing the blood of a normal white man with glue or gelatin." Isaacs[6] concluded:

> "Whether this change in shape of red blood-cells has any relation to the condition in sickle-cell trait or anæmia remains to be elucidated by further studies."

Another objection to Dr. Lehmann's statement is provided by Isaacs's observation that glue and gelatin act not only on the red blood-cells of the normal white man, but also on those of patients with sickle-cell anæmia, people with the sickle-cell trait, cats, dogs, chickens, frogs, and patients with spherocytosis, and on human nucleated red cells. He found that after mixing glue or gelatin with the blood, practically all the red cells immediately assumed "sickle" shapes, and that when the freshly sickled cells were examined under a cover glass, they became spherical, and finally fragmented and hæmolysed. But, as I mentioned in my article, the sickle cells in the trait or the anæmia usually revert to normal in wet preparations after 4 or 5 days. This again suggests that the changes produced in the red cells by colloids are quite different from those which occur during true sickling. In Isaacs's photomicrographs there was no sign of either the elongated form, with filamentous flagella at both ends, or any of the transitional forms, such as are seen in the trait or the anæmia.

The constriction of the finger, the high temperature, and the sealing with vaseline to prevent re-oxygenation and desiccation of the blood-drop, are simply factors which favour the manifestation of the sickling phenomenon; *they are not directly responsible for the change in shape of the red cells.*

In my article I pointed out that in the most severe degrees of the sickle-cell anomaly, all the red cells changed into the fully developed flagellated forms, even without constriction of the finger and, I would now add without sealing with vaseline and at room-temperature.

I have repeated some of Isaacs's experiments on the action of glue, gelatin, and some other colloidal substances—e.g., 'Glucine.' None of the forms seen during sickling can be simulated by the distorted cells produced by the instantaneous action of glue or gelatin.

The electron microscopy studies of Rebuck et al.,[7] and earlier observations with the optical microscope, have clearly shown the structure of the developmental forms in the sickle-cell anomaly, and underlined how the sickled forms differ from the distorted red cells produced by glue or gelatin. The same can be said for the sickle cells in dry smears.

The distorted red cells which can be seen concentrated at the edges of a normal blood film are, according to Isaacs, "blunt at one end, elongated and narrow at the other end (the end pointing at the outside of the film)," and they can be easily distinguished from the sickle cells of the trait or the anæmia. True sickle cells are found not only at the edges but throughout the film; their distribution resembles that of the white cells.[8]

These sickled forms have been reproduced in vitro by Shen et al.,[9] and the change under these conditions was irreversible.

Dr. Lehmann thinks that the vaseline *may* cause sickling; but the results obtained by the Itano-Pauling method, in which no vaseline is used, are against this. Again there is often a negative phase when no sickling may be found for months despite the use of vaseline.

Using the Itano-Pauling method in carriers of the trait or in patients with sickle-cell anæmia of high degree, I have observed that fresh preparations, made after constriction of the finger and kept at room-temperature, showed a more rapid development of flagellate forms (within 15 minutes to 2 hours) than preparations kept at 36°C without sodium metabisulphite. Moreover sealing with vaseline made no difference to the progress of sickling.

In carriers of the anomaly, examined at random from the population, or in patients with mild degrees of the anæmia, a few red cells changed to flagellate forms, while other fragmentated erythrocytes were unchanged. If vaseline is responsible it must have a selective action on ertain red cells—an action which should be equally pparent in all preparations. But when a person had a nild degree of the anomaly, usually only 1 out of 4–6 pecimens showed signs of sickling.

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[1] Perutz, M. F., Liquori, A. M., Eirich, F. *Nature, Lond.* 1951, 167, 929.
[2] Isaacs, R. *Science*, 1950, 112, 716.
[3] Perr, H. M. *Blood*, 1949, 4, 179.
[4] Scriver, J. B., Waugh, T. R. *Canad. med. Ass. J.* 1930, 23, 375.
[5] Itano, H. A., Pauling, L. *Blood*, 1949, 4, 66.
[6] Isaacs, R. *Science*, 1950, 112, 116.
[7] Rebuck, J. W., Woods, H. L., Monaghan, E. A. *Proc. Soc. exp. Biol., N.Y.* 1948, 68, 220.
[8] Langeron, M. Précis of Microscopy. Paris, 1942.
[9] Shen, S. C., Fleming, E. M., Castle, W. B. *Blood*, 1949, 4, 498.

This is one of the discrepancies between the Mediterranean næmia and that of the Negroes. Recent observations in Negroes have shown that all preparations (4 or 5 for each ndividual) were positive in 303 people out of 310.[9] In 6 eople there was no sickling in only 1 preparation, and in 1 ase 2 preparations showed no sickling.

Further evidence on the influence of racial admixture has been given by Hodges,[10] who has shown that sickling is commoner in pure Negro blood which has been diluted by small amounts of white and American-Indian blood.[11]

Athens. J. CAMINOPETROS.

SIR,—I have read the paper by Dr. Caminopetros in your issue of April 5, and feel compelled to try to dissipate any confusion to which it may have given rise.

The problem of the relationship between the hereditary hæmolytic anæmias, especially between Cooley's anæmia and sickle-cell anæmia, is a complicated one. There are many features common to both—namely, osteoporosis of the long bones, leg ulcers, hæmolytic crises, hypochromia and poikilocytosis of the red blood-cells, target cells, increased resistance to hypotonic saline solutions, slow erythrocyte-sedimentation rate despite the severe anæmia,[12] positive liver function tests,[12] and bilirubinæmia. Yet there are also distinct differences which permit us to regard these anæmias as separate disease entities. These differences are not only clinical and morphologic (typical mongoloid facies in Cooley's anæmia, sickling of red cells and pains in the abdomen and joint in sickle-cell anæmia) but also biochemical (normal electrophoretic pattern and very high alkali denaturation values of hæmoglobin in Cooley's anæmia,[13–16] in contrast to abnormal electrophoretic pattern and small alkali denaturation values of hæmoglobin in sickle-cell anæmia.[14 15 17]

In his paper, Dr. Caminopetros considers only the morphology of the two anæmias. According to him, patients with Mediterranean anæmia exhibit as a rule the sickling phenomenon. As far as we know, he is the only worker to make such an observation. We have repeatedly tested patients with Cooley's anæmia for sickling (over 25 cases) and have never found it positive, with the exception of 2 patients who were mixed cases —that is, who had one parent with the sickle-cell trait and one with the thalassæmia trait.

The difficulty of recognising a sickle cell in a dry smear is well known. Dr. Caminopetros finds them even in cases of sickle-cell trait—parents of anæmic patients not anæmic themselves (figs. 3 and 4)—who are not supposed to show sickle cells in a dry smear. Figs. 3 and 4 show, according to the author, sickle cells and oat cells. I do not see these in the photomicrographs. In smear 4 the red cells are obviously deformed.

Dr. Caminopetros says that he usually finds sickle cells at the edge of the end of the dry smear. Now everybody knows that in normal smears the red cells are many times elongated at the edge of the smear and that this is definitely an artefact.

The photomicrographs of the wet preparations (figs. 1, 2, 5, 6, 9) show sickle cells or their precursor forms. But how can one be sure that all the wet preparations that Dr. Caminopetros considers positive for sickling truly show sickle cells, when one considers the peculiar ideas of the author on sickle-cell morphology in general? Only thus can we explain the amazing finding of 49·1% sickling of the population of Athens. We have so far tested about 200 children with different diseases, coming from all parts of Greece but mostly from Athens, and have found[18] only 1 child with the sickle-cell trait and 3 with sickle-cell anæmia (these 3 children came from parts of Greece where the disease is known to be relatively common).

On the other hand, in a survey at the little town of Petromagoula, which is a focus of sickle-cell anæmia, we tested the blood of 1016 inhabitants taken at random; and in wet preparations we found sickling in 15%.[12] The frequency of the disease in this town was found to be 0·25%.[19] There are certainly other focuses of sickle-cell anæmia in Greece. The village of Marcopoulo is one of them, judging by Dr. Caminopetros's findings. The sickle-cell trait is no doubt common in these areas. But it takes courage—to say the least—to state that among the population of Athens, where the disease is practically non-existent, the frequency of sickling is 49·1%. It would exceed even the frequency in the Baamba tribe in Africa, which is 45%![20]

I will not enter into a discussion of other points with which I also disagree, such as the importance of admixture of Greek and Mongolian blood. Let me say only that other peoples of Europe and Asia (Hungarians, Turks, &c.) have been mixed with Mongols much more than the Greeks, and yet Cooley's anæmia is rare among them compared with Greeks or Italians.

In conclusion, although not denying that the two anæmias have features in common, the absence of sickling in Cooley's anæmia—a fact ascertained not only by us but also by Italian and American workers (the Cooley cases in America are after all also of Mediterranean origin)—and other important differences, require, I think, the differentiation of the two diseases. Dr. Caminopetros himself considers this separation necessary when he says: "Hence we must regard these anæmias as two distinct morbid entities."

In view of these facts I believe that the term proposed by the author—"drepanocytic anæmia of the Eastern Mediterranean"—should not be accepted.

University of Athens. C. CHOREMIS.

ARTIFICIAL RESPIRATION

SIR,—In your annotation last week you advocate the shelving of Schafer's method, and imply that in the correspondence subsequent to your leading article of March 15 much stress was laid on the value of the diaphragm. True enough this was mentioned as a possible heart stimulant, but this was by no means the main argument in favour of the retention of Schafer's method.

When Professor Schafer introduced his method, with the unchallenged advantage of the prone position, he competed with Silvester by introducing pressure on the back as a procedure which gave as much capacity variation of the thorax as did Silvester's manipulation of the thoracic muscles. Moreover, he demonstrated that back pressure, whilst the abdomen rested on a solid floor, forced up the abdominal contents, stretched the diaphragm, compressed the lungs (an important factor), and stretched some of the thoracic muscles. The elasticity of all the stretched muscles, including the diaphragm, allowed air to rush into the lungs as soon as pressure ceased. Any first-aider performing Schafer's method correctly, and not afraid of squashing the breath out of the lungs, sees the notable recoil of the chest muscles as soon as he releases pressure.

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10. Hodges, J. H. *Ibid*, 1950, 5, 804.
11. Neel, J. V. *Ibid*, 1951, 6, 389.
12. Choremis, C., Zervos, N., Constantinides, B., Zannos, L., Sklavounou, S. *Hellen. iatr.* 1951, 20, no. 12.
13. Sturgeon, P., Itano, H., Valentine, W. *Blood*, 1952, 7, 305.
14. Singer, K., Chernoff, A. J., Singer, L. *Ibid*, 1951, 6, 413.
15. Singer, K., Chernoff, A. J. Singer, L. *Ibid*, p. 429.
16. Zannos, L. Thesis submitted to the Medical School of Athens University on April 2, 1952.
17. Pauling, L., Itano, H. A., Singer, S. J., Wells, J. C. *Science*, 1949, 110, 543.
18. Choremis, C., Boubouli, M. To be published.
19. Choremis, C., Zervos, N., Constantinides, B., Zannos, L. *Lancet*, 1951, i, 1147.
20. Lehmann, H., Raper, A. B. *Nature, Lond.* 1949, 164, 494.

If only the medical profession would give an English translation to the American methods—e.g., Schafer hip lift and Schafer arm lift—all would be well. So many first-aiders have been trained in Schafer's back-pressure, prone-position method that it would be wrong to let them think that other methods are to be introduced. Surely, it would be easy for the first-aid lecturer to explain the rare occasions when the hip lift or arm lift should be added to their efforts. I say "rare occasions" since in the last twenty successful resuscitations of adults I have relied on Schafer's method, helped usually by an early whiff of concentrated carbon dioxide (as recommended by Prof. Yandell Henderson).

I have never had to use the arm lift in actual practice, although I teach it as a valuable adjunct to Schafer's method for those who are not robust enough to deal with a heavy patient.

Hemel Hempstead, Hertfordshire. GILBERT BURNET.

TEACHING EVOLUTION IN THE SCHOOLS

SIR,—Your annotation of April 26 expresses an opinion which is often heard nowadays. I should like to urge the opposite view—that the subject of evolution should be postponed, rather than advanced, in educational curricula.

Much of the value of such a unifying theory is lost when it is given before, or at the same time as, the descriptive or experimental facts it is designed to unify. It is far more impressive to have a satisfying explanation advanced when a large body of knowledge has already been assimilated, than to have the explanation imparted at once as a scaffold on which the knowledge is to be draped. Perhaps Professor Huxley would agree with this, but from his opinion that biological subjects "should be treated whenever possible from the evolutionary angle" it rather looks as if he advocates giving evolutionary teaching from the very first, concurrently with descriptive and physiological teaching. This does not seem to me the most effective way of teaching; and (which is more important) it leaves the young mind with the impression that the theories of evolution are on the same factual footing as their descriptive and physiological instruction. It is surely far better to carry on with straightforward physiology and natural history until a sufficient body of facts has been assimilated to enable the subtler question of evolution to be appreciated; and this may well be not till university days.

But there are wider and more serious objections still to Professor Huxley's programme.

In spite of all efforts to make it seem otherwise a child is likely to interpret the doctrine of evolution as meaning that man has just come by chance from lower animals, that he has originated without purpose, that human life has just "happened." I know that Waddington and others have made strenuous efforts to erect "evolutionary ethics," but will they grip the heart of a young boy or girl? What is likely to be the effect on a young mind of the teaching that progress has always been made by the triumphing of the fitter and stronger over the weaker—in effect by organisms saying "me first" and endeavouring to put it into practice by force? How are children and adolescents likely to react to the theory of sexual selection? I am not arguing that natural selection is untrue and ought to be consigned to the rubbish-heap; I am only trying to urge caution in implanting explosive ideas in minds so young and immature that they are quite at our mercy. If education of the young is to be designed first and foremost to build character, it is surely not a handicap, as your annotation suggests, but a positive advantage to postpone the teaching of evolution to university years.

I should like to make two other points. Students coming into this department are not seriously handicapped by *not having* had biological teaching given equal rank with physics and chemistry in their school years. In fact it is common to hear members of the staff expressing almost the opposite view; we find they are often weak in physics, chemistry, and mathematics, and we would rather they had a better grounding in these subjects. They will then be better qualified to grasp the difficult and momentous questions posed by living things.

Finally, whatever evolutionary teaching is given in schools should be balanced by an equal emphasis on the fact—which I think is becoming steadily more obvious—that Natural Selection or any other mechanism is quite inadequate by itself to explain the organic world. Biology, no less than the physical sciences, "demands creation."

How else can we account for the origin of life itself, for the suddenness of its appearance in the Cambrian (and in a highly organised form too), for the complete obscurity in which the origins of the great plant and animal phyla are shrouded, for the failure to find any really adequate mechanism to account at a sufficient rate for the immense differences we observe in living structures—not to mention the deep-seated moral and religious instincts of the human mind? How else can we make our children realise that biology does *not* teach that human life is the product of blind forces, originating without purpose and without assured goal, or that all we see and know of life is nothing but "the result of a single basic property of living matter: its not-quite-perfect capacity for self-copying"?

If we are to treat biological subjects "whenever possible from the evolutionary angle," then in common sense and fairness we must emphasise the creationary aspect as well. I think quite a large number of younger biologists believe the time is ripe for a return to the view that living things (to go no further) were created by God, but created with a propensity for variation which has resulted in a limited, though extensive, amount of evolution. This view alone, I firmly believe, does justice to all the facts.

Botany Department,
Imperial College of Science and Technology, London, S.W.7.
D. C. SPANNER.

SUBLINGUAL *d*-TUBOCURARINE FOR MUSCULAR SPASM

SIR,—Many authors have reported benefit from the injection of *d*-tubocurarine chloride for the relief of spasm of skeletal muscle in acute and chronic ailments.[1-5] Suspensions in oil and wax are usually given in order to prolong the effect of a single injection. With such preparations a dose of 25 mg. is commonly given in 1 ml. of suspension by intramuscular injection. Though relief may last for 24 or even 48 hours, undesirable effects may occur. Painful nodules at the site of injection are fairly frequent and symptoms of overdosage may sometimes be alarming. To avoid these disadvantages and to simplify the use of curare in chronic diseases, I decided to try sublingual administration. Tablets were prepared in several sizes and shapes containing various amounts of alkaloid.[6]

For most purposes a tablet about 3 mm. in diameter containing 2 mg. of *d*-tubocurarine chloride pentahydrate is best. It dissolves under the tongue in 3–10 minutes and in the cheek in 15–30 minutes. The taste is somewhat bitter, but patients have not complained.

Patients who had benefited from curare by injection were given sublingual tablets to assess the dose needed for comparable relief. Of 22 tested, all experienced equal relief from tablets taken sublingually. A few obtained adequate relief from one 2 mg. tablet, but more often it was necessary to give several tablets. In this series the largest dose required was 12 mg., but I have been told of a patient with acute back strain who required 20 mg. in the course of an hour. No

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1. Schlesinger, E. B. *Arch. Neurol. Psychiat.* 1946, 55, 530.
2. Weed, M. R., Purvis, D. F., Warnke, R. D. *J. Amer. med. As* 1948, 138, 1087.
3. Norcross, B. M., Robins, H. M., Lockie, L. M. *Ibid*, 1949, 140, 397.
4. Fuller, J. D. *Ibid*. 1950, 143, 789.
5. Margolis, H. M., Caplan, P. S. *Ann. intern. Med.* 1949, 31, 615.
6. Tablets were supplied by Brent Laboratories Ltd., 62, Avenue Road, Toronto.

igns of overdosage were reported. When the right dose was found, relief from pain or spasm was always rapid, nd was usually noticeable 2–3 minutes after the ublingual dose.

Relief lasted from 2 to 8 hours. Some patients with hronic disease found that the morning dose required was larger than those needed during the day—e.g., mg. in the morning, 4 mg. at noon, and 4 mg. in the ate afternoon.

The following cases are presented as typical or because hey illustrate reactions of special interest.

CASE 1.—A man, aged 51, had severe lumbar pain, probably aused by a slipped disc. Maximum straight-leg elevation was 45°. After 1 ml. (25 mg.) of oily suspension leg elevation ncreased to almost 90° and pain disappeared. After 40 hours ain returned, but was relieved by 6 mg. sublingually. He was kept on 14 mg. daily for 8 weeks when treatment could be stopped.

CASE 2.—A man, aged 66, had had severe low backache for 2 years with right-sided sciatic pain. Clinically he had a slipped disc (L 2–3 and L 3–4), confirmed by X-ray examination. 3 mg. of *d*-tubocurarine sublingually gave much relief from back pain, but sciatic pain was unaffected. 4·5 mg. given parenterally in aqueous solution had the same result.

CASE 3.—A man, aged 70, had undergone bilateral lumbar sympathectomy, and severe right-sided lumbar pain developed immediately after the operation. There was no relief from curare in any form or from physiotherapy. He was improved after 2 months' rest in bed.

CASE 4.—A woman, aged 52, had been almost crippled for 2 years by persistent slipped-disc pain. 3 mg. by injection in aqueous solution relieved pain within 3 min.; leg elevation increased from 40° to almost 90°. Relief lasted for about 8 hours, and pain was then less severe than usual. She was maintained on 14 mg. daily for 3 weeks and then all treatment could be stopped. She can now do housework and climb stairs, and is almost completely free from pain.

CASE 5.—A man, aged 45, had severe spasm of the anal sphincter after hæmorrhoidectomy. 1 ml. of a long-acting suspension gave complete relief for 72 hours. For 2 hours he had marked weakness and double vision. Later 4 mg. sublingually controlled pain for 24 hours, and after 2 weeks he was cured.

CASE 6.—A man, aged 47, with disseminated sclerosis had difficulty in walking and in focusing his eyes, and weakness of the hands and arms. He had not worked for 4 years. He is now back at work on 8–12 mg. of *d*-tubocurarine sublingually.

Pain due to inflammation, neoplasm, pressure on nerve-roots (case 2), or damage to vertebræ was not relieved by curare, but pain mainly caused by muscle spasm often stopped dramatically. The spasm of chronic neurological disease was often considerably reduced.

I have found it unnecessary to use the oily injection at all and it seems reasonable to hope that it may no longer be needed. The aqueous injection, however, remains indispensable. To each patient in whom a trial of curare seems warranted, I give an intramuscular injection of 1 ml. (3 mg.); if there is no substantial relief in 10 minutes, the patient is judged unsuitable for curare. With a favourable result the symptoms disappear and usually recur in 2–6 hours. The next day 1–2 tablets (4 mg.) are given sublingually and if there is no response within 5 minutes comparable to that following injection, another tablet is given every 5 minutes, up to a maximum of 12 mg., until relief is obtained. When the pain recurs 2 tablets (4 mg.) less than this established dose is given at once, and the patient is instructed to take 1 more tablet every 5 minutes until relief is obtained. Normally 2–3 doses daily suffice to control the pain and "repeat" doses are usually 2–4 mg. smaller than the initial "loading" dose or the first morning dose.

My thanks are due to Dr. J. T. Hauch, physician-in-chief, St. Joseph's Hospital, Toronto, for permission to include several cases under his care.

Toronto. A. ERDEI.

RELAXATION IN LABOUR

SIR,—The correspondence in your columns on this subject prompts me to mention that the greatest relaxation possible is achieved by means of the hypnotic state. The depth of effective hypnosis can vary from a light or medium trance to somnambulism. The important point is that, whatever the depth, instructions to the patient showing her how to relax are then more effective than they would be if given during normal consciousness. Not only is she enabled to relax more completely but, in reasonably good subjects, analgesia may also be obtained by means of post-hypnotic suggestion.

This method is receiving increasing attention from obstetricians in the U.S.A., who were stimulated to use it by the late Dr. J. B. deLee, regarded by many as the "father" of modern obstetrics. Dr. deLee stated that, in his opinion, "the only anæsthetic which is without harm is hypnotism"; and, in a recent American textbook,[1] "suggestive relaxation" under hypnosis is advocated as the ideal means of securing relief from pain in childbirth. I can also testify to its efficacy in the conduct of some of my own cases.

London, E.18. G. F. NEWBOLD.

VARICOSE ULCERS

SIR,—Your annotation of April 5 will do much harm by producing defeatism concerning chronic ulcers of the leg. I am not alone in still being delighted to see these cases, because they can be so simply cured with 'Elastoplast' or other compressive bandages, whether the venous incompetency is superficial or deep. There is no difficulty in deciding which it is: if the former, strategical ligations plus injections, simultaneous and possibly subsequent, clear up the cause and make cure final; if the latter, then permanent support may be necessary as the deep ligations are very disappointing.

Mr. A. C. Brewer, of Liverpool, has, I believe, cleared up the mystery. He has shown by arteriographic studies that the opaque medium appears four times as quickly in the femoral veins in these legs as in normal legs. The arteriovenous shunts are apparently opened by the back-pressure on the venous side, and tissues in the lower parts of the leg lose their capillary nutrition. Abolish this back-pressure by ligatures and injection for superficial incompetency or compressive bandages if the venous inadequacy is deep, and hey presto! the ulcers will heal and be kept healed.

One hard-working enthusiast with missionary zeal in each big town in this country will solve this ulcer problem, which still remains a reproach to our profession. These enthusiasts will never appear even in an over-registrared profession if a journal of your standing is so unjustifiably gloomy over what is really a simple problem, by suggesting bed rest as the only cure.

London, W.1. A. DICKSON WRIGHT.

SIR,—It would seem from reading this correspondence and your annotation that there is a difference of opinion as to the value of surgical procedures directed against the dilated superficial veins themselves. As diagnosis should precede treatment it is surprising that no-one has mentioned the efficacy of Perthes's test in sorting by easy clinical means such ulcers as may improve or be healed after surgical attack on the veins from such as may probably be made worse.

A useful procedure is to examine the ulcer with the leg up on a couch or footstool, then to ask the patient to stand and to elicit Trendelenburg's test if sufficient value is put to it. Then the veins are palpated and the presence of a cough impulse noted lower down the vein; this may indicate deep vein incompetence. The veins, if present, are now thoroughly distended, and it is a simple procedure to apply a venous tourniquet above the varicosities and to ask the patient to "mark time" as vigorously as the age and swelling allow. If the veins get softer to the feel two things are proven: (1) that the "leg-muscle pump" is functioning, and (2) that operative ligation can do no harm. If the veins do not change or get tauter, then surgery will almost certainly do harm.

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[1] Kroger, W. S., Freed, S. C. Psychosomatic Gynecology.

Phlebography, ascending and descending, can then be reserved for such few patients as may be considered to demand further surgical procedures, in order to complete the *investigations.*

The test does seem a most valuable and easy method of examining these troublesome cases, requiring at the most ninety seconds, an old pair of artery forceps, and a piece of rubber tubing.

It may not be possible to apply the test to Dr. McAusland's "waterlogged dropsical leg" (May 17) but its previous application may have prevented some of these legs from becoming waterlogged and dropsical. How often is a history elicited of previous ligation with no benefit!

London, S.W.15. P. A. LANE ROBERTS.

POSSIBLE DANGER WITH CYCLOPROPANE

SIR,—Dr. Russell's letter of April 26 renders a great service in reminding us of the danger if the cyclopropane key is accidentally knocked on without the knowledge of the anæsthetist in charge. This complication was, to the best of my knowledge, originally described by me in 1949 when I wrote[1] that "universal keys are the worst offenders in this respect as they stick out farther than those of the circular type." In anticipation of Dr. Weisz's suggestion (May 10) I added: "the remedy lies in taking the cyclopropane key off the cylinder when not in use."

During recent months a firm which specialises in the manufacture of anæsthetic apparatus has redesigned its key in accordance with my original suggestion; it is circular, has no protrusions, and is engraved on its upper surface with the words "remove when not in use." I have asked this firm to construct for me a safety-key which works on the principle of the "dead man's handle" used in driving trams and electric trains. Such a key would have a recessed spring and miniature clutch so that it would have to be pressed down before engaging the tap on the cylinder. Upon release, the key would spin round if knocked, without turning on the gas.

King's College Hospital,
London, S.E.5. A. H. GALLEY.

PREVENTION OF CORONARY THROMBOSIS

SIR,—When Dr. Shute recommended vitamin E as an anticoagulant in coronary thrombosis (Jan. 12), I objected (Feb. 2) that this vitamin had been found to have coagulant properties. Now in his answer (April 5) he confirms the findings of Prosperi and Tropeano and admits that a fresh thrombosis may develop in a patient taking large doses of α-tocopherol. It is true that soon afterwards he says that a slight increase in dosage will cause this thrombus to resolve, but he has not told us which dosage will accelerate the blood-clotting and which will promote resolution of the thrombus. Dr. Shute does not say what he means by "increasing the dose slightly," nor does he explain how he finds out the amount of vitamin E that is really effective.

While Dr. Shute warns against high dosage of α-tocopherol in hypertensive heart-diseases,[2] in the same issue of the same journal his associate Dr. Vogelsang[3] says: "I have never seen any harmful effects from the large scale administration of vitamin E to patients with hypertension or with rheumatic heart disease. I believe that their warning in regard to possible harmful effects in such patients is unnecessary." In a letter some time ago,[4] Dr. Shute called α-tocopherol "a physiological and safe anticoagulant"; but is it really so safe if by its use a fresh thrombus may be produced?

Rome. GUGLIELMO SBARIGIA.

EPILEPSY AFTER AN INJECTION

SIR,—An injection of crystalline penicillin which I gave the other day to a woman of 42 produced an alarming response.

I had been giving her penicillin for a urinary infection (500,000 units twice daily). She felt sick immediately after the first injection and there was a transient generalised erythema a few moments after the second, but no serious symptoms. After the third injection, however, the erythema recurred, she vomited twice, and she then lost consciousness. She became pulseless and grey and her breathing stopped. I was preparing to give adrenaline when she had a mild epileptiform convulsion accompanied by urinary incontinence. I gave the adrenaline, and after an anxious moment she breathed again. She regained consciousness in about ten minutes and has suffered no ill effects since.

She had had penicillin and other injections in the past without trouble. There was no personal or family history of epilepsy and no signs of organic disease of the nervous system.

It may be that this was the first attack of idiopathic epilepsy precipitated by the injection, or a convulsion associated with cerebral œdema; but I would be interested to hear of any similar reactions after crystalline penicillin.

London, W.11. RICHARD BELL.

WHAT SHOULD THE NURSE BE TAUGHT?

SIR,—May I, as the headmistress of a girls' secondary modern school, express my opinion concerning nursing employment for girls who leave school at 15.

I support with wholehearted conviction the letter (April 5) in which Dr. Cropper and Mr. Houghton express a truth which is only too evident—that unless girls who leave school and desire nursing as a career are absorbed at once into hospitals, the majority will be lost to the nursing profession.

At the end of each term an average of 5% of my "leavers" express a sincere desire to become nurses. They have attended junior Red Cross classes, and have passed tests in practical and written work. They are strong, practical, and capable young women who, through economic necessity, must earn a living. I feel sure that a training scheme could be devised whereby they could become useful auxiliaries, thus relieving the more skilled nurse of many duties which fatigue and lessen her efficiency for more exacting responsibilities. Surely in large modern hospitals there is room for the carefully selected 15-year-old girl who has difficulty in securing employment in a day-nursery *in order to mark time* for three years. Exploitation of such service would not be permitted in the progressive hospitals of today.

A simple uniform and a small salary would add dignity and give a sense of responsibility which, added to the girl's enthusiasm, would bridge the gap until training as a student nurse could start.

This is the considered opinion of my colleagues in the teaching profession. We are grateful to the Worcester doctors who have expressed the dire need for this reform, whereby all our best girls who leave school will not be absorbed into industry, but will in future find joy in service as nurse-cadets in our local hospitals. I would plead with hospital authorities to make this possible for the sake of the potentially good young nurses of the future.

Samuel Southall Girls'
Secondary Modern School,
Worcester. K. G. HUMPHREYS.

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[1] *In* Modern Practice of Anæsthesia, edited by Frankis T. Evans. London, 1949; chapter 19, p. 362.

[2] Shute, W. E. *Ann. N.Y. Acad. Sci.* 1949, 52, 354.

[3] Vogelsang, A. *Ibid.* p. 361.

[4] Shute, W. E., Shute, E. V. *Lancet*, 1950, i, 46.

Obituary

WILLIAM BROWN

M.A., D.M. Oxfd, D.Sc. Lond., F.R.C.P.

Dr. William Brown, formerly Wilde reader in mental philosophy and director of the Institute of Experimental Psychology at Oxford, died on May 17 at the age of 70. His approach to medical psychology was through the disciplines of mathematics and philosophy. He was aware of its wide implications and he believed that its application should be extended to international relations.

From Collyer's School, Horsham, he went to Christ Church, Oxford, where he was a scholar. He took honours in mathematical moderations in 1902 and in the final school of natural science and in literæ humaniores in 1905 when he was awarded a Locke scholarship in mental philosophy. After spending some time in post-graduate study in Germany be returned to London, where he studied the mathematical theory of probability under Karl Pearson. In 1910 he obtained his D.SC. Lond. and received the Carpenter medal. The following year he published his monograph on the *Essentials of Mental Measurement*. Meanwhile he was completing his medical studies at King's College Hospital and he qualified in 1914. In the same year he was appointed reader in psychology at King's College, a post which he held till 1921. But the outbreak of war in 1914 separated him almost at once from his new academic duties.

Of the years that follow M. C. relates: "In 1914 the war neuroses had taken neurologists and psychiatrists by surprise and there was nothing approaching the Army psychiatry that we saw in this last war. Into the gap thus formed stepped a little group of anthropologists and psychologists—W. H. R. Rivers, William M'Dougall, C. S. Myers, and Elliot Smith—who found a spiritual home at Maghull, where Major Rows carried on, first a hospital, and then a combined hospital and training centre with the efficient aid of Bernard Hart and Prof. T. H. Pear. Besides these there entered into the gap William Brown, a trained psychologist before he qualified in medicine, who had written in our professional journals about the treatment of patients by hypnotism. When he qualified he was already conversant with the problems of the psychoneuroses, and he quickly got special appointments in that domain. After a short spell in Alexandria he came back and spent six months with his fellows at Maghull. Later he became first resident medical officer at the newly opened Maudsley Hospital in London. In the autumn of 1916 he went to France, where he carried out the work that became the subject of much of his later writings—the restoration of shell-shocked men to front-line fitness by using abreaction under hypnosis. From March, 1918, till April, 1919, he was in charge of the Officers' Hospital at Craiglockhart."

When the war was over the anthropologists returned to their own affairs and William Brown was left undaunted, if alone. His appointment to the Oxford readership came in 1921, and from 1925 to 1931 he was also psychotherapist to King's College Hospital in London. But he still found time to write prolifically, and to this period belong the first editions of his books on *Psychology and Psychotherapy*, *Suggestion and Mental Analysis*, *Mind and Personality*, and *Science and Personality*. He was convinced of the recuperative value of neuromuscular relaxation in nervous and mental, and indeed physical, illness, and he regarded the use of suggestion in producing adequate relaxation as his own contribution to this method. In 1938 he described in the *British Journal of Psychology* his experiments demonstrating its effectiveness. His pen and his ideas both began to win wider professional recognition, and in 1930 he was asked to deliver the Terry lecture at Yale University. In 1930 he was also elected F.R.C.P., and the following year he was appointed director of the Institute of Experimental Psychology at Oxford. In 1935 he became president of the Society for the Study of Addiction, and last year he was president of the British Psychological Association.

The importance of psychology for the progress of social life and culture was one of his firmest beliefs, and he held that international conflict could be resolved by the same psychological means as he used in his practice. The approaching threat of war thus led him to a keen study of the personality of the Nazi leaders—he tried unsuccessfully to obtain an interview with Hitler—and many of his later writings discuss what he considered to be the hysterical and paranoid tendencies of the Führer. But in his *Oxford Essays in Psychology* (1948) he summed up all the truths for which he had striven. The work is perhaps more difficult to assess than the man, for as M. C. writes: "Medical psychology is still in a state of flux, and the full value of Brown's work is yet to be determined; but those who knew him will realise that he stood out well above the herd."

Dr. Brown's first wife, May Leslie Rayment English, by whom he had one son, died in 1916. His second wife, Dorothea Mary Stone, survives him with a son and two daughters.

Public Health

German Measles in Manchester

STARTING abruptly in the middle of February, there has been a large rise in the notifications of rubella in the city of Manchester. For the first six weeks of the year the average total was 64—about the usual figure for that time of year. But with the week ended Feb. 16, the totals rose sharply, and up to the end of April they had shown no sign of falling again.

—	Feb.		March					April			
Week ended	16	23	1	8	15	22	29	5	12	19	26
Notified cases ..	133	203	301	478	540	414	627	548	363	635	503

In these 11 weeks, the cases notified totalled 4745, giving a weekly average of 431. The age-distribution of cases in the first 17 weeks of 1952 was:

Age-group (yr.)	*Male*	*Female*	*Total*
0–4	675	652	1327
5–9	1280	1441	2721
10–14	221	343	564
15–19	51	101	152
20–24	29	54	83
25 and over	34	101	135

The number of cases notified in women in the child-bearing period (15–44) was 252, compared with 108 in men of the same age-group.

Variola Minor in South-east Lancashire

No case of variola minor has been notified from either the Rochdale or any other district since April 17. The World Health Organisation has been informed that the Rochdale area is now regarded as free of smallpox infection.

Paratyphoid B on the Welsh Border

On May 12 three sisters were admitted with food-poisoning to the isolation hospital at Bedwellty, Mon. As the girls had been ill for a week, it was too late to examine food samples. On the 14th the laboratory reported that *Salmonella paratyphi* B had been isolated from the eldest child. Six cases have now been confirmed in the Bedwellty area and three more are suspected. In the neighbouring district of Gelligaer fifteen patients have been definitely diagnosed and six others are suspect.

Repeated examinations of water-supplies, milk, artificial creams, meats, jellies, and cakes have so far failed to trace the source of infection.

Dr. R. A. Hoey, medical officer of health for Bedwellty, who kindly supplied details of cases in his district, says that it is difficult to see how one carrier can have infected all the cases, but the search for a common factor continues. We are also indebted to Dr. W. Bowen Owen, medical officer of health for Gelligaer, for telling us about the outbreak there. He reports that the patients are often constipated, but prominant rose-spots are a help in diagnosis. One of the many possible causes under investigation is some watercress which has been sold from door to door in the district.

Tuberculosis in Eire

In Eire the death-rate from tuberculosis in 1950 was 78 per 100,000 population, the lowest rate recorded in the country. In 1949 the rate was 91 per 100,000, while in 1948 it was 104.

This is recorded in the department of health's report for 1950–51,[1] which also mentions that during the year about 20,000 vaccinations were carried out under the auspices of the National B.C.G. Committee, and a further 4000 vaccinations under arrangements made by four health authorities. The fixed mass-radiography set operated by Dublin Corporation and the mobile set operated by Cork County Council took 15,329 and 11,437 miniature films, discovering about 145 and 31 cases of active tuberculosis.

During the year 396 additional beds were provided for cases of pulmonary tuberculosis in local-authority and voluntary institutions. The total number of hospital and sanatorium beds occupied by such patients at March 31, 1951, was 5236. The number of patients awaiting institutional treatment at that time was 509, compared with 770 a year previously.

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[1] *Report of the Department of Health, 1950–51.* Obtainable from the Government Publications Sale Office, G.P.O. Arcade, Dublin. Pp. 97. 3*s.* 6*d.*

Births, Marriages, and Deaths

BIRTHS

ALMOND.—On May 10, at the Radcliffe Infirmary, Oxford, to Joy (née Forster), wife of Dr. John M. C. Almond—a daughter.

BARRAS.—On May 10, at St. Mary's Nursing Home, Nottingham, to Kathleen (née Varden), wife of Dr. Brian Barras—a son.

DOBBIE.—On May 10, to Hazel (née Schooling), wife of Dr. D. N. Dobbie, 31, Westmoreland Road, Bromley, Kent—a son.

DRURY.—On May 9, at Stanley Nursing Home, Chester, to Joan (née Williamson), wife of Lieutenant M. Drury, R.A.M.C., Malaya—a son.

FALLON.—On May 14, at Royal Infirmary, Perth, to Hazel, wife of Mr. Martin Fallon, O.B.E., M.CH., F.R.C.S.I.—a son.

FERGUSON.—On May 9, at St. Johns Maternity Home, Ealing, to Olga, wife of Dr. S. C. Ferguson—a son.

FREW.—On May 11, at Fort House, Perth Road, Dundee, to Peggy (née Trechman), wife of Dr. J. S. Frew—a daughter.

GABB.—On May 11, at Oaklands Nursing Home, St. Leonards, to Lucie (née Smith-Bunney), wife of Dr. Headley Gabb—a son.

GAUNT.—On May 10, at Shearwood Nursing Home, Sheffield, 10, to Anne, wife of Dr. R. T. Gaunt, of Chesterfield—a son.

HOLLAND.—On May 14, at the London Hospital, Whitechapel, to Mary (née Carter), wife of Dr. E. Kennedy Holland—a daughter.

HOPE.—On May 6, at the Dilke Memorial Hospital, Cinderford, to Margaret, wife of Dr. T. A. Hope—a son.

JOHNSON.—On May 13, at the London Hospital, to Patricia (née Oliver), wife of Dr. Francis Johnson, of Bawtry, Yorks—a son.

REA.—On May 8, at Chipping Hill House, Halstead, to Agnes (née Fraser), wife of Dr. A. H. Rea—a son.

SARGENT.—On May 15, at Salisbury Infirmary, to Helen (née Mackoskey), wife of Dr. David Sargent—a daughter.

UNWIN.—On May 11, to Midge (née Slack), wife of Dr. Peter Unwin, Heathcot, Abbotskerswell, Newton Abbot—a daughter.

WEBB.—On May 7, at Brook Street Maternity Home, Ipswich, to Mary Helen (née Kelly), wife of Dr. Roy Webb—a daughter.

ZORAB.—On May 15, at the County Hospital, Winchester, to Wendy (née Milligan), wife of Dr. W. G. Zorab—a son.

MARRIAGES

BRENNAN—LAZARUS.—On May 17, at Blackheath, London, John Brennan, M.R.C.P., to Joyce Lazarus, D.OBST.

CRAN—HAWARD.—On May 14, at St. Stephen's Church, Westminster, Captain Ian Mitchell Cran, R.A.M.C., to Lavinia Joan Haward, of Hadlow Down, Sussex.

GRAY—HAMILTON.—On May 3, at Frankby Parish Church, Cheshire, T. D. Huon Gray, M.B., to Kathleen E. C. Hamilton, M.B.

JONES—REES.—On May 17, at Windsor, Edward Wilson Jones, M.B., to Hilda Mary Rees.

SEELIG—SALAMAN.—On May 8, in London, Siegfried Frederick Seelig, M.D., of 15, Wimpole Street, W.1, to Auriol Elizabeth Salaman.

DEATHS

AHERN.—On May 15, in Cheltenham, David Ahern, D.S.O. and Bar, L.R.C.P.E., colonel, R.A.M.C. retd, aged 74.

BROWN.—On May 17, at Ascot, Berkshire, William Brown, D.M. Oxfd, F.R.C.P., of 88, Harley Street, W.1.

CARR.—On May 14, at Ellesborough House, Butler's Cross, Donald William Carr, M.D. Camb., aged 86, for many years C.M.S. medical missionary in Persia.

CLIFFORD.—On May 16, at 69, Gainsborough Road, Finchley, N.12, John Hudson Clifford, M.B. Aberd., aged 59.

CRELLIN.—On May 15, at Harrogate, Douglas Crellin, M.C., B.A., M.R.C.S.

GARDENER.—On May 14, William Frederick Gardener, M.R.C.S., of 19, Glenluce Road, Blackheath, late of Sydenham, aged 88.

HALPERIN.—On May 2, Jacob Halperin, M.R.C.S., D.O.M.S., aged 43.

HARWOOD.—On May 13, at Fernhill, Normandy, Surrey, Leonard Austin Harwood, M.R.C.S., L.D.S., late of 90, Sloane Street.

MALLAM.—On May 10, William Andrew Mallam, M.R.C.S., formerly of Hampstead and Naples.

MARTLAND.—On May 2, Edward Norman Martland, M.B. Manc., colonel, R.A.M.C. (T.A.) retd.

Appointments

BALL, W. A., M.B. Lond.: appointed factory doctor, Petworth district, Sussex.

CRAMOND, W. A., M.B. Aberd., D.P.M.: deputy physician-superintendent and asst. psychiatrist, Kingseat Hospital, Newmachar, Aberdeen.

DURKIN, SHEILA, M.B. Aberd., D.P.H.: asst. M.O.H. and asst. school M.O., Smethwick.

GALLOWAY, ROSA, M.B. Edin.: asst. M.O.H. and asst. school M.O., Bolton.

GAVIN, F. W., M.D. Edin., D.P.H.: M.O.H. and asst. county M.O., Richmond, Yorkshire.

GODFREY, R. C., M.B. Adelaide, M.R.C.P.: senior resident M.O., King's College Hospital, London.

HAY, R. K., M.D. Belf., D.P.H.: M.O.H. and divisional M.O., Stapeley, Nantwich.

HUTCHISON, DOUGLAS, M.B. Glasg.: member of staff of the regional M.O., Scottish region of British Railways, Glasgow.

WELPLY, N. C., M.R.C.S.: asst. anæsthetist (S.H.M.O.), hospitals of the Aylesbury and district H.M.C.

WOOD, H. L.-C., M.S. Lond., F.R.C.S.: consultant orthopædic surgeon, Royal Masonic Hospital, London.

East Anglian Regional Hospital Board:

BARKER, E. M., M.D. Witwatersrand: surgical registrar, West Norfolk and King's Lynn General Hospital.

DIXON, R. I., M.R.C.S., D.A.: asst. anæsthetist, Peterborough hospital group.

ELLERKER, A. R., L.M.S.S.A.: anæsthetic registrar, Newmarket General Hospital.

MCCREANOR, J. D., M.B. N.Z.: medical registrar, United Norwich Hospitals.

RIPMAN, H. A., M.B. Lond., F.R.C.S., M.R.C.O.G.: consultant obstetrician and gynæcologist, East Suffolk and Ipswich area.

ROMAGNOLI, A., M.D. Florence: anæsthetic registrar, Peterborough Memorial Hospital.

Liverpool Regional Hospital Board:

DODD, BESSIE, M.B. Lpool, M.R.C.O.G., D.P.H.: consultant obstetrician and gynæcologist, hospitals in the East and South Liverpool groups.

HENNESSY, D. P., M.B. N.U.I., D.P.M.: whole-time asst. psychiatrist, *Upton Mental Hospital.*

RAWCLIFFE, RACHEL, M.B. Lpool: whole-time consultant pathologist, hospitals in the Birkenhead group.

Sheffield Regional Hospital Board:

DOYLE, J. O., M.D. N.U.I., M.R.C.P.I.: asst. venereologist to area consultant.

MAMAK, JAN, M.D. Lwow., D.A.: asst. anæsthetist, Boston group of hospitals.

WASS, N. H., M.D. Belf.: asst. chest physician, Grimsby area.

South-East Metropolitan Regional Hospital Board:

BURTENSHAW, J. M. L., M.A., D.M. Oxfd, D.P.H.: asst. pathologist, Medway and Gravesend group.

FARQUHARSON, MARY, M.A., M.D. Camb., M.R.C.P., T.D.D.: consultant chest physician, Lewisham group.

FRANCE, W. G., M.B. Leeds, F.R.C.S.: consultant orthopædic surgeon, Lewisham and Sidcup and Swanley groups.

HAYNES, W. N. L., M.R.C.S., D.P.M.: consultant psychiatrist, Oakwood group.

HORLEY, J. F., M.B. Lond.: asst. pathologist, Brighton and Lewes group.

KENNY, SHEILA, M.A., M.D. Belf., D.M.R.D.: asst. radiologist, Medway and Gravesend, Dartford, and Mid-Kent groups.

LLEWELLYN SMITH, S. H., B.A., B.M. Oxfd, M.R.C.P.: consultant physician, Lewisham group.

MARSH, J. M. K., D.M. Oxfd: consultant chest physician, Camberwell group.

MEADE, F. B., M.B. Lond., M.R.C.P.: asst. chest physician, Brighton and Lewes group.

SEWELL, R. H., CH.M. Manc., B.SC., F.R.C.S.: consultant orthopædic surgeon, Greenwich and Deptford group.

WHATLEY, ELIZABETH, M.B. Lond., B.SC.: consultant psychiatrist (child guidance).

The Hospital for Sick Children, Great Ormond Street, London:

DIGGLE, J. H., M.B. Manc., B.SC., M.R.C.P., D.C.H.: house-physician.

MACLEAN, R. S., M.B. Edin., L.D.S.: dental house-surgeon.

TAYLOR, D. G., M.B. Belf.: house-surgeon, orthopædic and plastic departments.

Western Regional Hospital Board:

FERGUSSON, A. G., M.D. Glasg., F.R.F.P.S.: part-time dermatologist-in-charge, Stobhill Hospital, Glasgow.

GARDINER, T. B., M.B. Glasg., F.R.F.P.S.: asst. orthopædic surgeon, Western Infirmary/Killearn Hospital.

HARRIS, WALDRON, M.R.C.S., D.O.M.S.: asst. ophthalmologist, Stirlingshire.

JACK, J. B., M.B. Glasg., F.R.C.S.E., F.R.F.P.S.: asst. orthopædic surgeon, Western Infirmary/Killearn Hospital.

MCCARDEL, J. D., M.B. Glasg., F.R.F.P.S.: asst. orthopædic surgeon, Victoria Infirmary, Ayrshire.

WHITE, W. F., M.B. Glasg., F.R.C.S.E., F.R.F.P.S.: asst. orthopædic surgeon, Royal Infirmary/Law Hospital.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Notes and News

FIFTH WORLD HEALTH ASSEMBLY

The assembly continued its discussions in Geneva last week. A resolution urging the World Health Organisation to undertake a programme of leprosy control was passed at a meeting of the committee on programme and budget. An attack on dental caries was advocated by Dr. S. S. Savonen (Finland); he said that the eating of sweets was the foremost cause of the high caries-rate among European school-children. The committee approved the formation of further expert committees to advise W.H.O. in 1953; the subjects to be studied include poliomyelitis and rheumatism.

The assembly gave Dr. C-E. A. Winslow, professor of public health in the University of Yale, the Léon Bernard Foundation medal and prize, which is awarded for "an outstanding contribution to the progress of social medicine."

It was unanimously agreed that Tunisia and Morocco be admitted as associate members of W.H.O.

ANIMAL-MAN RELATIONSHIP IN TROPICAL DISEASES

At a meeting of the Royal Society of Tropical Medicine and Hygiene on May 15 Mr. James Carmichael, D.SC., instanced a number of diseases shared by animals and man in Africa. Tuberculosis is common in the long-horned Ankole cattle of Uganda, and he has found evidence of its spread from them to man; but even in the people living most intimately with their cattle tuberculosis is ordinarily caused by the human type of *Mycobacterium tuberculosis.* Of the virus diseases, rabies is prominent. rinderpest has an indirect bearing on human welfare, and Rift Valley fever and yellow fever are of direct importance to man. The rickettsial diseases are also important, but the diseases which have most caught the imagination are the protozoan infections due to the trypanosomes. Dr. Carmichael urged that the method of controlling trypanosomiasis by destruction of game, with the object of depriving the tsetse flies of their preferred food, should be judged on its merits, without the violent prejudice which it sometimes attracts. Veterinarians, no less than others, are lovers of animals, and are loth to adopt severe measures without good cause.

Dr. H. D. Burke-Gaffney emphasised the unity of many problems of human and animal health, and pointed out that the World Health Organisation list of diseases common to both contains 80 names. Dr. P. C. C. Garnham traced the progress of several insect-borne diseases, which, when they accidentally spill over to man, acquire different vectors, and may even lose them altogether. The cycle in plague is rodent-flea-rodent, but when man is infected by a flea the cycle may become, in pneumonic plague, man-man without the intervention of an arthropod vector. Relapsing fever has in places taken the course rodent-ornithodorus-rodent-ornithodorus-man-louse-man.

A DOCTOR'S LIFE

Who Leaves the Crowd,[1] an American novel written by a practised hand, tells of an unworldly doctor, Henry Baker, who worked, with his wife Liz, for twelve years to find a new mould to cure tuberculosis; it opens on the eve of a medical meeting where Henry read a paper on his work, and goes on to tell of the consequences to his career and to his marriage. Whether or not the author is herself a doctor, she understands well the domestic side of medical life, and the strains and stresses of marriage, as well as the uncertainties and anxieties of research.

A REVIEW OF MYCOLOGY

A journal published by the Commonwealth Mycological Institute contains abstracts of papers on medical and veterinary mycology from the world's periodicals. First issued in 1943 as the *Annotated Bibliography of Medical Mycology*, its name has now been changed to the *Review of Medical and Veterinary Mycology*. The *Review* will appear twice a year; the annual subscription is 10s. Inquiries should be addressed to the Director of the Institute, Ferry Lane, Kew, Surrey.

Conference on Hospital Contributory Schemes

The annual conference of the British Hospitals Contributory Schemes Association (1948) will take place in Cardiff on Thursday and Friday, Oct. 23 and 24. Dr. Ffrangcon Roberts will be one of the speakers.

University of Oxford

In a congregation held on May 1, the degree of D.M. was conferred on I. V. Polunin.

University of Cambridge

On May 10, the following degrees were conferred:

M.D.—J. F. Buchan, R. H. Ellis, P. G. Mann, J. H. Simpson, R. S. Stevens.

M.B., B.Chir.—D. W. Hall.

University of Sheffield

Mr. P. A. King has been appointed tutor in surgery and lecturer in general surgery to dental students, Dr. J. Mackinnon research assistant in medicine, and Dr. R. M. H. McMinn demonstrator in anatomy. Mr. J. Duncan Gray has also been appointed part-time lecturer in diseases of the ear, nose, and throat, and Dr. J. W. Brown part-time lecturer and clinical teacher in medicine.

The J. G. Graves medical research fellowship has been awarded to Dr. P. G. Walker.

Queen's University, Belfast

The senate, jointly with the Northern Ireland Hospitals Authority, has appointed Dr. G. M. Bull to the chair of medicine, and Dr. J. J. Pritchard to the chair of anatomy.

Dr. Bull, who is 34 years of age, was educated at the University of Cape Town where he graduated M.B. in 1939. After qualifying he was for a time assistant in the department of medicine there. After coming to this country he took the M.R.C.P. in 1947, and the same year he proceeded to his M.D. Cape Town. He has since been appointed lecturer in medicine at the Postgraduate Medical School at Hammersmith. He is also medical liaison officer to the South African Council for Scientific and Industrial Research. His research interests have been mainly in the field of renal disease.

Dr. Pritchard took the degree of B.SC. at the University of Adelaide in 1934, and the same year he was awarded a Rhodes scholarship He continued his medical studies at the University of Oxford and at St. Bartholomew's Hospital, qualifying in 1940, and taking his B.M. the following year. He held house-appointments under the E.M.S. and at Barts before he became junior demonstrator in anatomy at University College. Later he was appointed to his present post of reader in human anatomy in the University of London at St. Mary's Hospital. He has published papers on the distribution of alkaline phosphatase in the pregnant uterus of the rat and on fracture repair in frog, lizard, and rat.

Faculty of Radiologists

The annual meeting of the faculty will be held at Newcastle upon Tyne on June 20 and 21.

International Hospital Congress

The International Hospital Federation will hold their congress next year in London from May 25 to 30.

Faculty of Ophthalmologists

The following have been elected officers for 1952–53: president, Mr. O. M. Duthie; vice-presidents, Mr. R. C. Davenport and Mr. A. B. Nutt; hon. secretary, Mr. J. H. Doggart; hon. treasurer, Mr. E. G. Mackie.

Alex Simpson Smith Lecture

Mr. Murray A. Falconer will deliver the Alex Simpson Smith lecture on Thursday, June 19, at 8.30 P.M., at the West London Hospital, Hammersmith Road, W.6. He will speak on the Future of Surgery in the Treatment of Intracranial Hæmorrhage.

Hunterian Society

The subject chosen for the 1952 gold medal essay is the Management of Hypertension in General Practice. The competition is open to *all* general practitioners, and further details may be had from the hon. secretary, Mr. Alec W. Badenoch, 110, Harley Street, London, W.1.

Ministry of Health

The Minister of Health has appointed Mr. Graeme Finlay, M.P., to be his parliamentary private secretary. He has also appointed Mr. A. R. W. Bavin to be his principal private secretary, and Miss P. M. Ibbotson to be his assistant private secretary.

Research into Nursing Problems

A Boots research fellowship in nursing has been instituted in the University of Edinburgh. It is attached to the department of social medicine. In collaboration with representatives of the Royal College of Nursing, a list is being prepared of problems that might profitably be investigated. The fellowship need not be held by the same person for the whole of the seven years for which it is available. Candidates need not be medically qualified, but preference will be given to doctors if they also have qualifications suitable for the work to be carried out.

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[1] By Mildred Walker. London: Stanley Paul. 1952. Pp. 224. 10s.

Society for the Study of Addiction

Dr. P. O. Wolff will deliver the Kelynack lecture on Tuesday, June 10, at a meeting of this society at the Westminster Medical School, Horseferry Road, London, S.W.1. He will speak on the Activities of the World Health Organisation in Drug Addiction.

Socialist Medical Association

The association is holding a national tuberculosis conference on June 28 and 29 at Battersea Town Hall. Further particulars may be had from Dr. Hugh Price, secretary of the tuberculosis campaign committee of the association, 86, Rochester Row, S.W.1.

Ophthalmological Prize

The council of the Ophthalmological Society of the United Kingdom has instituted the Treacher Collins prize (£100) which is to be awarded triennially for the best essay on a subject selected by the council. The subject for the next award is the Eye in General Vascular Disease. Essays should reach the hon. secretary of the society, 45, Lincoln's Inn Fields, London, W.C.2, not later than Dec. 31, 1953.

Committee on Poliomyelitis

The Royal College of Physicians of London has set up a committee "To provide those working on the ætiology, epidemiology, prevention, and treatment of poliomyelitis with opportunities for the exchange of information and the discussion of common problems." Those interested in these problems are asked to write to Dr. W. Ritchie Russell, secretary of the committee, at the college, Pall Mall East, S.W.1.

Education of Handicapped Children in Scotland

A Working Party has been set up under the chairmanship of Dr. John Jardine by local-authority associations in Scotland and educational and medical bodies to consider the reports issued by the Advisory Council on Education in Scotland on the education of physically and mentally handicapped children, and of those who are socially deprived. The Working Party will suggest how best a coördinated plan on a national basis can be evolved to help every handicapped child no matter where he lives. The Working Party ask that the results of any recent inquiries and investigations should be sent to their secretary, Mr. James B. Frizell, City Education Department, 12, St. Giles Street, Edinburgh, 1.

Harveian Society of London

The Buckston Browne-Gray Hill dinner of this society was held at the Royal College of Surgeons on May 15. Dr. James Barnett, the president, replying to the toast of The Society, proposed by Sir Harry Brittain, said that very little was known about the private life of William Harvey, but it was possible to get some glimpses of it from 17th-century writings, and particularly from Pepys. One of the interesting facts that emerged was that Harvey, as physician to the court of Charles I, had been entitled to three meat dishes at every meal. Mr. D. N. Matthews, an honorary secretary of the society, welcomed the guests, and recalled that in 1902 Sir Harry had been a founder member of the Pilgrims' Society, and had done a great deal to encourage coöperation and friendship in the English-speaking world. Sir William Haley, director-general of the B.B.C., replying to Mr. Matthews, thought that in 30 years of broadcasting the handling of medical subjects had been one of the biggest responsibilities of the B.B.C.; and the coming of television had made that responsibility all the greater. Sir Cecil Wakeley, P.R.C.S., also spoke for the guests, and commended the society for its progressive attitude.

EMERGENCY BED SERVICE.—In the week ended last Monday applications for general acute cases numbered 930. The proportion admitted was 91%.

CORRIGENDUM: *Directory and Catalogue of Collections of Micro-organisms maintained in Canada.*—In our review of March 29 we stated that this catalogue was not for sale. We now learn that copies may be had from the National Research Council, Ottawa, Ontario, Canada ($2.50).

The British Standards Institution (24, Victoria Street, London, S.W.1) has prepared draft standards for mental-hospital bedsteads (CO(M)531) and for adult cots (CO(M)532), and a draft revision of B.S. 1694 for children's cots (CO(M)530). Comments on these drafts should reach the institution before June 27.

Diary of the Week

MAY 25 TO 31

Monday, 26th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. R. I. S. Bayliss: A.C.T.H. and Cortisone.
ROYAL EYE HOSPITAL, St. George's Circus, S.E.1
5 P.M. Dr. T. H. Whittington: The Squinting Child.
INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hi
S.E.5
5.30 P.M. Dr. E. Stengel: Lecture-demonstration.
MANCHESTER MEDICAL SOCIETY
9 P.M. (University of Manchester.) *Section of General Pract*
Dr. John Kerr: Influence and Status of General Practi
(Presidential address.)

Tuesday, 27th

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P.M. (Hammersmith Hospital, W.6.) Mr. Kenneth Bowe
The Elderly Primigravida.
ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
3.45 P.M. Mr. H. Spencer: Bronchial Cancer. (Erasmus Wils
demonstration.)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. Dr. Donald Hunter, Dr. R. Schilling, Dr. M. W. Goldbla
Dr. A. Thelwall Jones, Dr. C. N. D. Cruickshank: Clini
Aspects of Occupational Disease.
ROYAL EYE HOSPITAL
5.30 P.M. Mr. R. P. Crick: Fundus Appearances in Vascul
Disease.
ST. BARTHOLOMEW'S HOSPITAL PHYSIOLOGICAL SOCIETY, E.C.1
8 P.M. Sir Adolphe Abrahams, Prof. J. L. D'Silva, Prof. T.
Cureton, Mr. W. D. Coltart, Dr. J. Etheridge, Mr.
Wint: Problems Arising Out of Athletic Training.
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospit
Medical School, W.2
5 P.M. Prof. C. M. MacLeod (New York): Almroth Wrig
lecture.
INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Stre
W.C.2
5.30 P.M. Dr. J. A. Dudgeon: Viral Diseases.
UNIVERSITY OF BIRMINGHAM
4 P.M. (Medical School.) Dr. Boris Ephrussi (Paris): Nucle
and Cytoplasm in the Genetics of Micro-organisms. (Fi
of three William Withering lectures.)

Wednesday, 28th

POSTGRADUATE [illegible]
11.45 A.M. [illegible] ference.
CHARING CROS [illegible] 62, Chandos Pla
W.C.2
5.30 P.M. Dr. George W. Corner (Washington): Events of t
Primate's Ovarian Cycle. (Huxley lecture.)
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Superficial Fungous Infectio
UNIVERSITY [illegible]
4 P.M. [illegible] l Cytoplasm in the Geneti
of [illegible] of three William Witheri
lectures.)
UNIVERSITY OF GLASGOW
8 P.M. (Department of Ophthalmology.) Dr. Fergus Campbell
Night Myopia.

Thursday, 29th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. Stephen Gol [illegible]
LONDON SCHOOL OF HYGIE [illegible]
5.30 P.M. Prof. C. M. [illegible] Reactio
in Pneumococci.
ROYAL EYE HOSPITAL
5 P.M. Dr. S. Nevin: *Ocular Aspects of the Diagnosis of Cerebr*
Tumours
ST. [illegible] HOOL, Hyde Park Corner, S.W
5 [illegible] rology lecture-demonstration.
WE [illegible] DISEASES
5.30 P.M. (Department of Psychiatry, 48, Cosway Street, N.W.1
Dr. E. A. Bennet: Psychological Methods of Treatmen
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Dudgeon: *Viral Diseases.*
UNIVERSITY OF OXFORD
8.30 P.M. (Wingfield-Morris Orthopædic Hospital.) Prof.
Wiberg (Lund): Shelf Operation in Congenital Dysplas
of the Acetabulum and Subluxation and Dislocation
the Hip.
UNIVERSITY OF BIRMINGHAM
4 P.M. Dr. Ephrussi: Nucleus and Cytoplasm in the Geneti
of Micro-organisms. (Last of three William Witherin
lectures.)
UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Dr. J. C
Broom: Leptospirosis.

Friday, 30th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
11.15 A.M. Surgical clinical-pathology conference.
2 P.M. Sir Heneage Ogilvie: Abdominal Surgery.
4 P.M. Dr. W. D. M. Paton: Ganglionic Block.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. G. B. Dowling: *Tuberculosis and Sarcoid.*
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Ro
W.C.1
4.30 P.M. Mr. C. Gill-Carey: Diseases of the Nose and Nas
Sinuses.
EUGENICS SOCIETY
5.30 P.M. (Royal Society, Burlington House, W.1.) Mr. N. W
Pirie, F.R.S.: Biochemistry of Conception Control.

any single vessel or even the vessels along both borders provided the section ligatured is not longer than the breadth of the stomach at the point of section. Surgeons have attributed leakage from the duodenal stump to excessive mobilisation and devascularisation of the duodenal walls. But this is usually caused by the reverse fault—inadequate mobilisation, leading to insufficient invagination with sutures that are too tightly passed through the wrong structures.

The blood-vessels reach the two borders of the duodenum in the greater and lesser omenta, which are the remains of the dorsal and ventral mesenteries, and the walls should be free between these omenta. In practice the *right* wall is usually free, unless disease has glued it to other structures, but the peritoneal relations of the upper, left, and lower walls are highly variable. *Above*, the gall-bladder has often grown into the ventral mesentery, so that a cholecystoduodenal fold replaces the free border of the lesser omentum. *Below*, the origin of the right end of the greater omentum tends to overlap the right wall of the duodenum to a variable extent, and must be detached before the line of the inferior duodenal vessels is reached. On the *left* an open lesser sac and a peritonealised duodenum are uncommon, and there are usually fine adhesions binding the duodenum to the head of the pancreas.

FUNCTIONS

In function, the first part of the duodenum clearly differs as profoundly from the other parts as they do from the rest of the small intestine. Forty years' radiographic study has established that the first part is a holding segment, retaining barium for some time after it leaves the stomach, producing in films the typical ace-of-spades appearance of the duodenal cap, and then contracting suddenly and shooting its contents onwards. The remainder of the duodenum appears to be a passage way only, rushing the meal round to the duodenojejunal flexure and into the intestine in one rapid sweep; segmentation movements are not seen, and antiperistalsis occurs only when there is distal obstruction. The movements of the first part have been compared to those of diastole and systole in the chambers of the heart; they are more comparable to those of the pharynx. As the pharynx collects a bolus, after the mouth has chewed it up, and then shoots it down the œsophagus into the stomach, so the duodenal bulb collects a bolus of chyme after the stomach has churned it up, and shoots it round the remainder into the intestine.

DUODENAL ULCER

I find it difficult not to raise my eyes occasionally from the little island which I have chosen to explore, and scan the oceans that lie around it. A psychologist who suddenly shouted the word "duodenum" into the ear of a surgeon would get the automatic response "ulcer." Can we find in the structure and functions of the first part of the duodenum any clue to the ætiology of ulcer? I spoke just now of scanning oceans, but it requires a very tough Noah, steering an ark loaded up with pairs of research-workers and laboratory animals, and guided by a dove equipped with radar, to find an Ararat in the flood of ulcer literature. I wish, however, to put forward three simple statements that I believe everyone will accept: (1) peptic ulcers are found only in parts of the alimentary tract normally exposed to free hydrochloric acid, or in organs or structures abnormally brought into contact with it; (2) all normal men and women have free hydrochloric acid, but very few get ulcers; and (3) if the first two axioms are accepted, the cause of peptic ulceration must lie in an increase in the digestive action of the gastric juice, in an alteration in the time relations between its secretion and the presence of food in the stomach, or in an interference with the mechanism that protects the normal mucosa from attack. But even in the presence of increased acid or altered secretory rhythm it is almost necessary to postulate some failure in the local mechanism of protection before an ulcer can develop.

Need we go far to seek such a mechanism? We can see lesions appearing on every epithelial surface that we can look at with our eyes or through an endoscope. We see them on the skin, the tongue, the throat, the trachea, the œsophagus, the rectum, the colon, and the urinary bladder. They are due to many different causes. They come and they go, but if they were constantly exposed to a powerful digestive ferment they would not go. We do not often see acute lesions in the stomach, but since we look for them only when hæmatemesis or some other symptom calls attention to their presence we do not know how common they are. We know, at any rate, that the drugs we can buy at any store will cause them. An acute ulcer undoubtedly provides a breach of the normal protective surface, one that allows the access of gastric juice to the unprotected layers beneath. Yet the view that chronic peptic ulcers start as acute ulcers has not gained much support, chiefly because acute ulcers are found scattered over all parts of the stomach, whereas chronic ulcers are found only on the ulcer-bearing areas—the middle three-fifths of the lesser curve of the stomach and the first inch of the duodenum.

Is there anything in these areas that would explain why acute ulcers, which heal elsewhere, should persist in them? The explanation lies not in any fanciful arterial inadequacy, nor yet in exposure to trauma, but merely in their immobility. The lesser curve of the stomach is almost a fixed sling, extending in a radiogram from the left transverse process of the eleventh thoracic vertebra to the right transverse process of the second lumbar vertebra. It varies in length and curve in different people, but in each person it remains very much the same whether the stomach be empty or distended. When a meal is taken, the fundus and body stretch, but not the lesser curve; when a meal is digested, waves of peristalsis pass along the greater curve and the whole pyloric antrum, but not along the ulcer-bearing part of the lesser curve. The ulcer-bearing part of the duodenum is likewise distinguished from the remainder by its immobility.

The mucosa of the stomach and duodenum is adapted, as is the skin over various parts of the body, to the movement in which it is called on to participate. The skin over the belly is loose to accommodate meals, wind, and babies; that over the back need not be, and is not loose. The mucosa over the lesser curve of the stomach is smooth and comparatively fixed to the underlying muscles. The mucosa over the body and greater curve is thrown up in folds that, when seen through a gastroscope, resemble the surface of the brain; it moves freely over the muscle coats, being separated from them by a loose areolar submucous layer in which the blood-vessels run in slack loops. In the duodenum we see the same differences. The mucosa over the first or reservoir part is smooth and fixed and, when the duodenum is cut across, all the layers remain together. The mucosa lower down is so loose that he would be a rash surgeon who would guarantee to find the bile papilla in the opened duodenum without a probe in the common bile-duct to guide him.

I therefore suggest that, whereas breaches of surface are occurring constantly on all epithelial surfaces, they are liable to become converted into chronic lesions only when they are exposed to gastric juice, when they remain open long enough for gastric juice to attack the deeper layers, and when that gastric juice contains free hydrochloric acid. Outside the foregut and in an anacid stomach, digestion does not take place; outside the ulcer-bearing areas of the foregut the breach of surface is sealed by falling together of the loose mucosa before digestion can get to work, just as a tear in the loose areas of skin will heal before infection gets a start.

As surgeons we are called on to attack the first part of the duodenum for three indications: cancer of the stomach, gastric ulcer, and duodenal ulcer. In the first two conditions the duodenum is normal and the operation easy; in the third the duodenum is unhealthy and the operation seldom easy; it may be straightforward, it may be difficult, it may even be impossible, and it is a wise surgeon who recognises the impossible task before he undertakes it. Physicists may argue what would happen if an irresistible force were to meet an immovable body; surgeons know that when an incomparable technician meets an insoluble problem, the insoluble problem wins.

GASTRECTOMY

For Cancer

In gastrectomy for cancer the duodenum should be divided at least an inch beyond the pylorus, a simple matter, but the main need is a thorough clearance of the gastroduodenal aggregation of lymphoid tissue. While we are making this thorough clearance, the ultra mobile duodenum, which seems to be making our task easy, may land us into difficulties, for the head of the pancreas comes up with the duodenum. Twice recently I have recognised only just in time that the large vein I was about to divide beyond the glandular field was the superior mesenteric and not the right gastro-epiploic, as I had imagined.

For Gastric Ulcer

In gastrectomy for gastric ulcer, clearance of the duodenum is even easier than in cancer, for many gastric-ulcer patients are of the visceroptotic type, and division just beyond the pyloric ring is all that is required. The long and unscarred duodenum can thereafter be anastomosed to the stomach in the Schoemaker modification of the Billroth I gastrectomy, giving a result as nearly perfect as anything can be in gastric surgery.

For Duodenal Ulcer

In gastrectomy for duodenal ulcer it is necessary to mobilise and divide a duodenum deformed, distorted, and fixed to some degree by present or past ulceration, and to close the duodenal stump, for a duodenum that has once suffered ulceration should not be anastomosed to the stomach, however much reduced in size.

Is it necessary to remove the duodenal ulcer itself? On the grounds of cure, certainly not, for a duodenal ulcer will heal rapidly and remain healed permanently from the moment that it is removed entirely from contact with acid gastric juice. It is necessary to say "removed entirely," for gastro-enterostomy and full-width gastrectomy of the Polya type do not confer permanent protection on the ulcer site. It is often urged that recent or active hæmorrhage is an indication for excision of the ulcer that has bled. I disagree; indeed I hold that recent or active bleeding from a chronic duodenal ulcer is a contra-indication to a direct attack. The ulcers that bleed so severely that they demand an emergency operation to save the patient's life are usually large posterior ulcers in old men.

Proximal ligation of the gastroduodenal artery is seldom possible, for the point where it should be ligatured is usually buried in the œdematous scar tissue that surrounds the ulcer, and the attempt to secure it more proximally is apt to lead to injury of the main hepatic artery. Dissection round and past a large posterior ulcer is difficult and exacting even when done at leisure, but when it is attempted in a hurry in a patient who is bleeding and being transfused it is apt to leave the surgeon with a large torn artery, an injured common bile-duct, an unclosable hole in the duodenum, and a difficult interview with a widow.

In a necropsy specimen that I have seen demonstrated after such a tragedy the ulcer extended below the bile papilla. If the ulcer is not actually bleeding when the duodenum is exposed at laparotomy, the duodenum should be divided and closed in the simplest possible manner with the least disturbance of the ulcer. It will not bleed again, or if it does it will not bleed for long. If the ulcer is bleeding, as shown by the dark colour of blood seen through the duodenal wall, it should be exposed by a longitudinal incision through the pylorus, and plugged with firm pressure on a small tampon, while blood is run rapidly into a vein. After ten or fifteen minutes, when the systolic pressure has been sufficiently restored, the tampon is lifted off, and the hole or holes in the artery, probably closed by clot, can be seen. The holes are under-run with silk sutures, the duodenum is divided proximally and closed, and the gastrectomy is proceeded with.

On the technical grounds of neat closure of the duodenal stump it is clearly preferable that the duodenum should be divided distal to the ulcer. In most operations undertaken in a symptom-free period on a fit patient this is possible. When the ulcer site is so scarred and so fixed that it seems doubtful whether sufficient healthy duodenum can be exposed beyond the ulcerated zone (for in such cases the ulcers are usually multiple), the alternative of proximal duodenal division and closure is seldom possible. These are the duodena with pre-stenotic diverticula, the so-called clover-leaf deformity, and the divided cuff can seldom be invaginated safely into the stenosed isthmus that succeeds it. Division and closure of the stomach across the pylorus with radical resection proximal to this point, so-called exclusion gastrectomy, form an easy but disastrous way out, for where the pyloric mucosa is left behind to call up delayed gastric secretion recurrent ulceration is almost inevitable. Two alternatives remain (fig. 2): (A) prepyloric section with removal of all the pyloric mucosa, the valuable but slightly untidy procedure introduced by Bancroft, and (B) exclusion gastrectomy as a temporary expedient. If the abdomen is reopened six weeks after such an exclusion operation, the adhesions and œdema that prohibited

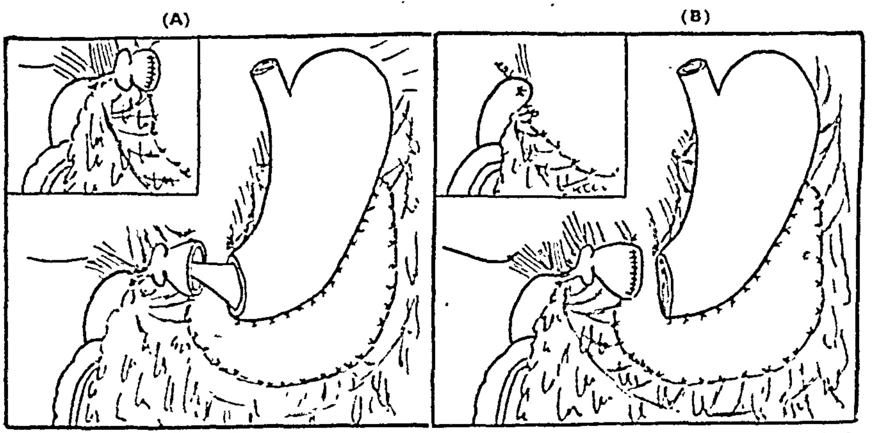

Fig. 2—Two ways of avoiding a difficult duodenal closure. (A) Bancroft's operation: prepyloric section of the outer coats of the stomach, with excision of the pyloric mucous membrane down to the pyloric sphincter. *Inset.* Closure of the outer coats over the pylorus. (B) Two-stage resection: *first stage, prepyloric section with closure of distal end. Inset.* Second stage, six weeks later, when pyloric stump is removed and the duodenum closed. In each operation the body of the stomach is removed as a radical gastrectomy.

duodenal dissection at the first operation will be found to have melted away, and removal of the pyloric-stump with division and invagination of the duodenum will be found to be a simple and relatively minor undertaking.

Many ingenious operations have been described for closing the duodenum at or just distal to an ulcer, for repairing holes that have been torn in attempting the impossible—in short for getting out of those difficulties into which we should never have landed ourselves. These methods, or many of them, will be found illustrated in Nissen's (1945) excellent book. Someone said that the best way to prevent milk from turning sour is to leave it in the cow; certainly the best way to deal with duodenal difficulties is not to seek them. When I fly the Atlantic I like a pilot who is not an expert at getting out of flat spins or landing on icebergs.

The decision whether to dissect out beyond a duodenal ulcer or not is one that must be made early. I believe that the right place to start a gastrectomy, for whatever indication, is well to the left, where the territories of the two epiploic arteries adjoin. Here stomach and colon can be lifted right up, here the lesser sac is opened where it is a big cavity, and after it is opened the mesocolon can be got away, the middle colic artery can be pushed out of danger, and, above all, the duodenum can be inspected from the left as well as the right, and felt from behind as well as from in front. It may appear that safe removal of the duodenum is impossible because it is so fixed to surrounding structures, particularly above, that dissection may endanger the common bile-duct or the hepatic artery, because there is so much œdema of the head of the pancreas that the duodenum lies in a rigid collar that will prevent invagination, or because the ulcer can be felt through the anterior wall to extend too far down. In such cases one of the methods of proximal closure must be chosen, but the decision must be made early. While the last two vessels on the gastric side of the pylorus remain unligatured a Bancroft operation is still possible, but when they have been divided there is no going back.

To speak to surgeons about the details of duodenal dissection and closure would be like telling golfers about one's brassie shot at the 14th. We all have our methods and we are all sure that they are the best. I change mine at least twice a year, and continually congratulate myself that I have at last reached finality. I believe that duodenum should be invaginated only into duodenum, never into head of pancreas. Pancreatic tissue is apt to ooze blood when stitches are passed through it, and to spit trypsin on to the suture line, and I am sure that the highest mortality from stump leakage is found in the patients of the pancreas-stitchers. Believing this I believe that at least half an inch of healthy duodenal wall should be cleared beyond the point of proposed section, to allow double invagination. Finally, I believe that clamps should be avoided, but that the duodenum should be cut across and its edges picked up with a purse-string suture of fine linen thread, which is then buried by two subsequent purse-string sutures of catgut. A duodenal stump so cut across never leaks while it is open, an observation that casts considerable doubt on the theoretical basis of many unsound gastric operations —that there is a normal reflux from the duodenum into the stomach.

Lastly I should say that, just as God is on the side of the big battalions, so he is on the side of the surgeon who never does an unnecessarily difficult operation. Most of the difficulties connected with the surgery of the first part of the duodenum are due not to the fact that there has been repeated ulceration but to the activity of the ulcer at the time of operation. We should not attempt a thyroidectomy on a patient with thyrotoxicosis until we had brought him, by careful preoperative measures, as nearly as possible to a temporary state of normality. In the same way we should never be led, as I am afraid we are often led, into operating on a patient with an active peptic ulcer if we can possibly avoid it; but by a period of careful medical treatment, of which rest in bed is the most important constituent, we should ensure that when we operate we are operating on the site of an ulcer rather than on an ulcer, and that our difficulties are those of avascular scar tissue rather than of the œdema and hyperæmia of active inflammation.

REFERENCES

Horton, B. T. (1928) *Amer. J. Anat.* 41, 197.
Nissen, R. (1945) Duodenal and Jejunal Peptic Ulcer. London.
Retzius, A. (1855) *K. svenska VetenskAkad. Forh.* May.

ANALYSIS OF REPORTS ON THE INFUSION OF DEXTRAN SOLUTION *

W. d'A. Maycock
M.B.E., M.D. McGill
From the Lister Institute, Elstree, Herts

After the publication of an account of a preliminary clinical trial of dextran (6% solution in 0·9% sodium chloride)† as a plasma substitute (Bull et al. 1949), the Ministry of Health, on the advice of the Medical Research Council, provided dextran solution for distribution to civilian hospitals through the regional transfusion centres. The medical departments of the Army and Royal Air Force also agreed to use some 1500 bottles in their hospitals.

The present report briefly describes what is known of the use of this dextran, the results obtained, and the untoward reactions which have been reported.

MATERIAL AND METHOD

Dextran

The dextran solution was prepared to a specification (see appendix) drawn up by the Blood Transfusion Research Committee of the Medical Research Council, and, to begin with, each batch submitted by the makers was tested for conformity to specification, the work being shared by the National Institute for Medical Research, the Medical Research Council Burns Unit, and the Lister Institute of Preventive Medicine. Later, only one batch in five was tested, and finally only batches selected at random were examined. Of the forty-eight batches making up the first 10,000 bottles, two were rejected because the renal excretion-rate in rabbits was above 25%, and four were rejected because they were pyrogenic to rabbits. With the agreement of the Committee, one of these pyrogenic batches was "reprocessed" by the makers to remove pyrogens; retesting showed that it was no longer pyrogenic, and it was released for use. So far reports have been received of 20 patients to whom this batch has been given, and of these 1 patient only has exhibited a febrile reaction (grade I, Riddell's classification). Six bottles of this batch before "reprocessing" were given to 5 selected patients, and, in spite of the fact that this solution had given a pronounced pyrogenic reaction by the standard rabbit test, it caused no rise of temperature in the recipients.

Report Cards

A report card was attached to each bottle with spaces for names of patient and hospital; clinical condition necessitating infusion; reactions to infusion (pyrogenic, grades I–III in Riddell's classification, pain, urticaria, other untoward reactions); records of temperature, blood-pressure, and pulse-rate after infusion; comments.

It was not expected that all the cards would be returned to the Medical Research Council Transfusion

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* A report to the Blood Transfusion Research Committee of the Medical Research Council.

† Manufactured by Dextran Ltd., Aycliffe, Darlington

Research Committee, but it was hoped that a sufficient number would be filled in and sent back to allow an opinion to be formed of the general efficacy of this dextran solution as a plasma substitute, and to give some idea of the frequency of reactions following its use. The great limitations of a trial arranged in this way were recognised by the committee—the multiplicity of observers, the varying standards of observation, the inability to avoid complicating factors such as mixed transfusions of blood, plasma, dextran, and crystalloid solutions—but it was thought that, if the solution were not effective or had harmful or serious results, these facts would be quickly reported.

Up to April 1, 1952, report cards have been returned of 2436 bottles derived from 49 batches, which have been given to 1647 patients, including Servicemen (Army and R.A.F.).

Patients

Of the 1647 patients, 557 were obstetrical cases, mostly postpartum hæmorrhage and similar emergencies; 905 were surgical cases; and 185 were cases of such miscellaneous conditions as nephritis, œdema, and marasmus (including patients in whom the condition necessitating transfusion was not reported). The 905 surgical patients are subdivided into 691 patients given dextran during or after operation, 105 given dextran to prepare them for operation (mostly cases of trauma), and 109 with burns. Many of these burns patients have been discussed by Bull (1951), who found that the mortality in a series of patients treated with an amount of dextran equivalent to the calculated plasma volume and then with plasma did not differ from that in a group treated solely with plasma.

RESULTS

The reports indicate that dextran has been used successfully as a plasma substitute. Many of the reports are brief and merely state "a good response," "a satisfactory restoration of blood-pressure"; others are more detailed, and the blood-pressure records in these suggest that this solution of dextran will restore and maintain a depleted blood volume. In many of the patients the infusion of dextran preceded the transfusion of blood or plasma.

Reactions were reported in 31 patients (1·88%). The types of reaction are shown in table I.

TABLE I—TYPES OF REACTION TO DEXTRAN

—	Pyrexia			Pain	Urticaria or other reaction
	Grade I	Grade II	Grade III		
No. of patients exhibiting reaction	8	2	5	5	15
Percentage of total number of patients	0·48	0·12	0·30	0·30	0·91

Apart from the grade-I and grade-II febrile reactions, the significance of which is difficult to assess, the remaining 16 reactions were reported in 25 patients (1·51%).

Of the grade-III reactions only one was severe. A sharp rigor, accompanied by cyanosis, sweating, and fall of blood-pressure, followed the infusion of one bottle of dextran. The previous day the patient had been operated on for a perforated appendix and had been given a bottle of dextran of the same batch without ill effect. 46 other patients have received 90 bottles of this batch without harm.

Of the 5 complaints of pain (in loins or head) 4 were associated with the earlier batches of dextran; the 5th followed the infusion of one of the later batches and was associated with a grade-I febrile reaction. In all these patients the infusion was reported as being beneficial.

9 cases of mild generalised urticaria were reported; 1 patient exhibited "marked œdema of the eyelids."

TABLE II—REACTIONS TO DEXTRAN BY BATCHES

Batch no.	Mild urticaria and œdema of eyelids	Severe reaction	No reaction	
			No. of patients	No. of bottles
A	1	–	1	1
B	2	–	137	181
C	1	–	55	84
D	2 (1 œdema of eyelids)	1	85	116
E	–	2	45	56
F	2	–	78	95
G	1	1	57	78
H	1	1	37	45

One patient vomited and complained of severe hea ache for a week after infusion of dextran.

4 other patients had a severer type of reaction characterised by vasomotor collapse, profuse sweating, coughing, vomiting, and cyanosis; and intense hyperæmia of the arms and face in 1 case, incontinence and muscula spasm in 1 case, severe pain in the loins in 2 cases, an severe pain in the chest and œdema of the face, eyelids and hands in 1 case. One of these patients, who had carcinoma of the cervix, acute enteritis, and cachexia and was in extremis, died shortly after receiving 5-1 ml. of dextran. The necropsy report stated: "In view of the post-mortem findings, anaphylactic shock remain a possibility. . . . I am not entirely satisfied about the œdema of the brain and the clot in the pulmonary artery not being the cause of death." No explanation of these reactions can be offered. In 1 instance the residue of th dextran used was infected; but, since the bottle had been opened, and several days had elapsed before it was examined, no conclusions can be drawn. Possibly th patients who reacted were sensitised by *Leuconostoc mesenteroides*, which synthesises dextran, or by antigenically related organisms—e.g., pneumococcus typ II or XX, but no evidence to support or refute thi suggestion can be offered. None of these severer reaction or of the urticarial reactions occurred in Servicemen.

The batches of dextran with which these severe reactions and the urticarial reactions were associated were infused without reaction into a large number of patients as table II shows.

Apart from the 1 doubtful case mentioned above, no deaths have been attributed to the use of dextran, and there have been no reports of pulmonary œdema or of delayed undesirable effects.

Among 16,206 report cards on bottles of blood and packed red cells received at one regional transfusion centre there were 123 grade-I febrile reactions (0·75%), 36 grade-II reactions (0·22%), 36 grade-III reactions (0·22%), and 31 urticarial reactions (0·18%). In another series, of 1882 report cards on bottles of blood and packed red cells used in one hospital and more closely observed by the regional transfusion centre there were 5 grade-I reactions (0·25%), 1 grade-II reaction (0·05%), 15 grade-III reactions (0·8%), and 2 complaints of pain. Among 1007 report cards on bottles of dried plasma there were 2 grade-I and 1 grade-III reactions. The general incidence of reactions following the use of dextran thus seems to be similar to that seen after the use of blood, and somewhat greater than that observed after the use of dried plasma. The incidence of the urticarial and severe types of reaction is similar to that of urticaria reported by DeGowin and Hardin (1940) in 2433 blood-transfusions.

Some of the batches of dextran have been stored for twelve months at Aden in an ambient temperature of 87°–98°F without causing detectable chemical or physical changes.

USE OF DEXTRAN

It should be unnecessary to recall that dextran does not contain protein or red cells; yet some report cards ate that it has been used in the treatment of “ hypo-roteinæmia ” and “ anæmia.” Dextran is likely to find s main use in restoring a depleted blood volume, when r some reason the natural fluids, blood and plasma, are ot available or are available only in insufficient amounts. t should be used with discretion. Infusion of too much extran will cause excessive dilution of plasma-protein, hich is probably undesirable, or of red cells which is bviously undesirable. For these reasons it is probably ise to limit the amounts of dextran infused to 2 or 3 ottles in patients with hæmorrhage and to 5 or 6 bottles correspondingly less in children) in burns patients, blood r plasma being used to complete the transfusion.

Appendix

The following tests for pyrogenicity, antigenicity, renal xcretion, and physical and chemical analysis were erformed:

Test for Pyrogens

20 ml. per kg. body-weight of the sample of dextran solution nder test was injected intravenously into each of three abbits of the same breed, each rabbit weighing 2·5–3·5 kg. The sample was regarded as pyrogen-free if the rectal temperature of each rabbit did not rise more than 0·6°C in the first four hours following the injection.

Tests for Antigenicity

(1) *Production of precipitins in rabbits.*—Dextran 0·6 ml. was injected into the marginal ear vein of each of two rabbits weighing 2·5–3·5 kg. at intervals of two or three days until nine injections had been given. From twelve to fourteen days later 5 ml. of blood was collected from the ear vein into a sterile tube and allowed to clot. Successive fourfold dilutions from 1 : 5 dextran were made in 0·9% sterile saline solution up to 1 : 20.480. These were tested against equal volumes of undiluted rabbit serum; control mixtures of serum and saline solution, and dextran and normal rabbit serum were also set up. The tubes were incubated for two hours at 37°C and read after standing at room-temperature for twenty-two hours.

(2) *Anaphylactic reaction in guineapig.*—Dextran 0·5 ml. was injected intraperitoneally into each of six adult guineapigs on three occasions at intervals of two days. Dextran 0·2 ml. was injected rapidly by the intravenous route into each animal, three guineapigs being thus tested fourteen days after the first intraperitoneal injection, and the other three twenty-one days after the intraperitoneal injection. Each guineapig was observed for the appearance of abnormal symptoms for thirty minutes after the test injections and again twenty-four hours later.

Tests for Toxicity

Dextran 1 ml. was injected intravenously into the tail vein of each of two mice weighing 16–25 g. A control mouse was given intravenously 1·0 ml. of sterile 0·9% saline solution.

Tests for Sterility

The tests were those laid down in S.R.O. no. 633, 1931 (Therapeutic Substances) paras. 16(b), 17(b), 19, 19(2), 19(3), 20.

Molecular Composition

(1) *Average size.*—The material was rejected if the intrinsic viscosity, determined at 37°C, was outside the range 0·32 ± 0·03.

(2) *Proportion of small molecules.*—The material was rejected if a twenty-four-hour urine sample following the injection of 20 ml. per kg. of body-weight into a rabbit weighing 2·5–3·5 kg. contained more than 25% of the dextran injected.

Chemical Analysis

The material was rejected unless it met the following conditions: dextran 6·0 ± 0·5 g. per 100 ml., sodium chloride 0·9 ± 0·05 g. per 100 ml., potassium less than 22 mg. per 100 ml., reducing power of sugars less than 100 mg. per 100 ml., and acetone less than 0·02%.

REFERENCES

Bull, J. P. (1951) *Proc. int. Congr. Blood-Transfusion* (in the press).
— Ricketts, C., Squire, J. R., Maycock, W. d'A., Spooner, S. J. L., Mollison, P. L., Paterson, J. C. S. (1949) *Lancet*, i, 134.
DeGowin, E. L., Hardin, R. C. (1940) *J. Amer. med. Ass.* 115, 895.

SALICYLATES AND NEURO-ENDOCRINE STIMULATION

H. VAN CAUWENBERGE
M.D. Liége

H. BETZ
M.D. Liége

From the Department of Internal Medicine and Laboratories of Chemical Research and Pathology, University of Liége, Belgium

A PREVIOUS paper reported that in rheumatic patients continuous salicylate therapy increases the urinary excretion of reducing steroids but has no regular effect on the urinary excretion of neutral 17-ketosteroids (Van Cauwenberge and Heusghem 1951a, 1952).

In healthy students an important decrease in the number of circulating eosinophils, and a significant increase of the urinary uric-acid creatinine ratio were observed after a single oral dose or an intravenous injection of sodium salicylate (Roskam et al. 1951).

In our experiments on rats the hæmatological, histological (Betz and Van Cauwenberge 1951), and biochemical signs of adrenal depletion (Van Cauwenberge and Heusghem 1951b) were observed after an intraperitoneal injection of an isotonic sodium salicylate solution (500 mg. per kg. of body-weight). These changes were identical with those seen in Selye's alarm syndrome and similar to those that follow an injection of A.C.T.H.

These experiments are in agreement with those of Kelemen et al. (1950), Robinson (1951), Champy and Demay (1951), and Hetzel and Hine (1951).

The hæmatological, histological, and biochemical signs of adrenal depletion are not seen either in adrenalectomised or in hypophysectomised animals after an injection of the same dose of sodium salicylate; but hypophysectomised animals respond to an injection of A.C.T.H.

Harris (1950) and Hume (1949) have stated the importance of the control exerted by the hypothalamus on the pituitary gland. Pain and emotional factors may affect the anterior lobe by way of the hypothalamic centres. We were thus led to investigate whether salicylates exert their effect by direct stimulation of the pituitary or by a neuro-endocrine mechanism. For this purpose we used rats anæsthetised with ‘ Dial ’ and then injected with a single dose of sodium salicylate. This led us to further study of the minimal dose of sodium salicylate necessary to stimulate the pituitary-adrenal axis.

FIRST GROUP OF EXPERIMENTS

Method

We used albino male rats weighing 150–200 g., fed on a standard diet, and kept at constant temperature.

Of 84 rats 10 acted as controls; 18 received an intraperitoneal injection of 0·6 ml. per kg. body-weight of a solution containing 100 mg. of dial per ml., being thus anæsthetised for at least eight hours, and were killed in groups of 3 at the first, second, third, fourth, sixth, and eighth hours; 38 rats similarly anæsthetised received an intraperitoneal injection of an isotonic sodium salicylate solution (pH 7·3) 500 mg. per kg. body-weight, fifteen minutes after anæsthesia had developed, and were killed in groups of 8 at the first, second, third, and fourth hours and by groups of 3 at the sixth and eighth hours; 9 rats similarly anæsthetised received A.C.T.H. 1 mg. per 100 g. body-weight and were killed in groups of 3 at the first, second, and third hours; and 9 non-anæsthetised rats were similarly treated with A.C.T.H.

The amounts of ascorbic acid and of cholesterol in the adrenals, the number of circulating eosinophils, the blood-salicylate level, and the histology of the adrenals, lymph-nodes, spleen, and thymus were studied in each rat.

Ascorbic acid was extracted from the adrenals with metaphosphoric acid and titrated against a solution of 2·6 dichlorophenol-indophenol. Only one adrenal gland is required for this.

Total cholesterol was estimated by photometry after its extraction from crushed adrenal tissue with ethyl alcohol followed by Liebermann's reaction. Only half an adrenal gland is required for this.

The *circulating eosinophils* were counted on blood drawn from the rat's heart when it was killed.

made by the direct eosin method using Dunger's fluid. The blood was withdrawn in three white-cell pipettes, and six counts were made on each specimen of blood in four double-celled Fuchs-Rosenthal counting-chambers.

The *plasma-salicylate level* was estimated in the mixed plasma of 3 or 4 rats by an unpublished method of Van Cauwenberge.

Histological technique: thymus, cervical lymph-nodes, and spleen were fixed in Bouin's fluid and stained with hæmatoxylin/eosin and by Masson's trichromic method. Adrenals were fixed in formalin and stained with scarlet red or Sudan III.

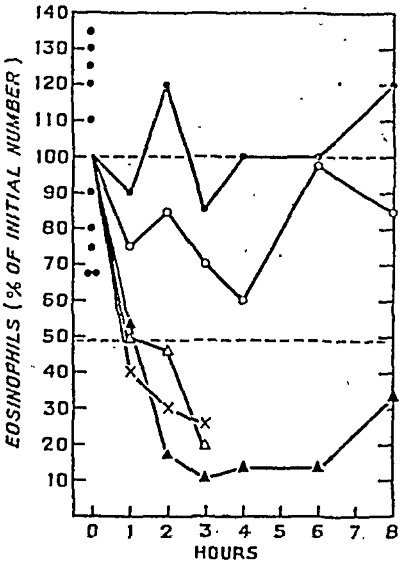


Fig. 1—Change in number of circulating eosinophils.

Results

Our results are summarised in figs. 1–3.

Fig. 1 shows that the *circulating eosinophils* did not vary more than 20% either way after dial injection alone. A decrease of more than 70% of the initial number was observed in normal and dial-anæsthetised rats injected with A.C.T.H., and of 40% when dial anæsthesia was followed by a sodium salicylate injection. A decrease of more than 80% of the circulating eosinophils was seen in intact rats injected with a similar dose of sodium salicylate.

Fig. 2 shows that no significant change in *ascorbic acid* of the adrenals was observed after dial injection. An important decrease was observed in normal and anæsthetised rats injected with A.C.T.H. There was no *significant* change in the ascorbic-acid value when dial injection was followed by sodium salicylate. A decrease of more than 50% was observed in intact rats injected with sodium salicylate.

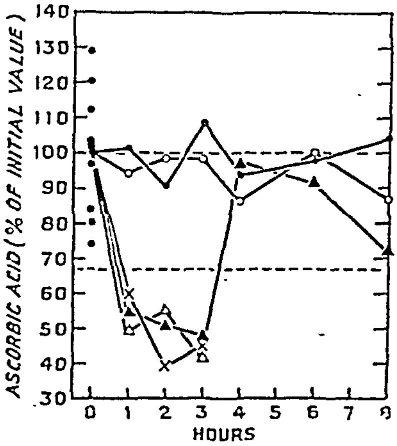


Fig. 2—Change in amount of ascorbic acid in adrenals.

Fig. 3 shows that, after dial injection, there was no significant change in the *cholesterol* content of the adrenals, but there was an important decrease when dial anæsthesia was followed by A.C.T.H. A fall of 35% was observed after dial injection followed by sodium salicylate, and a decrease of more than 60% in intact rats injected with sodium salicylate or with A.C.T.H.

●—● Dial-anæsthetised rats
○—○ " " " injected with salicylate
△—△ " " " " " A.C.T.H.
×—× Normal rats injected with A.C.T.H.
▲—▲ " " " " salicylate

* The values between the two dotted lines are not significant. The difference in the mean value is less than twice the standard deviation $\left(\sigma = \sqrt{\frac{\Sigma n(x - \bar{x})^2}{n}}\right)$

In all the animals injected with sodium salicylate 500 mg. per kg. body-weight the mean blood-salicylate level was 40–45 mg. per 100 ml. at the second hour after the intraperitoneal injection.

Histologically dial injection alone had no significant effect on the lipid contents of the adrenal cortex. After sodium salicylate injection alone, an important decrease of the lipids was observed in the zona fasciculata. The adrenals of rats injected with sodium salicylate after dial anæsthesia did not show any apparent depletion of the lipid contents.

Sodium salicylate injection produced in the thymus, lymph-nodes, and spleen very numerous nuclear pyknoses of lymphocytes, whereas dial injection alone had no effect on these cells. Sodium salicylate injection, even after dial anæsthesia, produced in the lymphoid tissue pyknotic lesions which appeared two or three hours after the injection and reached a maximum after about six hours (fig. 4).

Conclusion

The response observed after A.C.T.H. injection was identical in intact rats and in dial-anæsthetised ones.

The number of circulating eosinophils did not decrease and the ascorbic acid of the adrenals was not depleted, when sodium salicylate was injected into dial-anæsthetised rats.

The amount of cholesterol in the adrenals was less decreased after the injection of salicylate in animals anæsthetised by dial than in intact ones, but several histological signs of adrenal activity were seen.

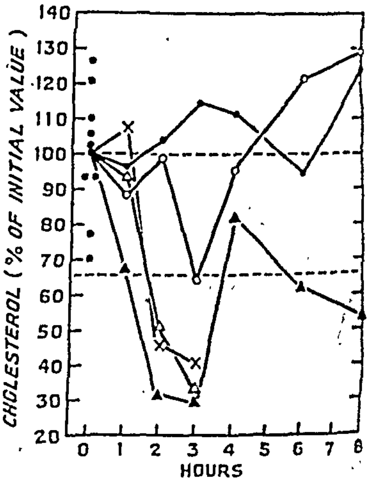


Fig. 3—Change in amount of cholesterol in adrenals. The curve for rats injected with sodium salicylate are from *Comptes Rendus de la Societe de Biologie* and are included here for comparison.

SECOND GROUP OF EXPERIMENTS

Method

Rats similar to those of our first group of experiments were used.

Of 98 rats, 10 acted as controls; 12 were injected intraperitoneally with an isotonic solution (pH 7·3) of sodium salicylate 300 mg. per kg. body-weight and were killed in groups of 4 at the first, second, and third hours. 16 rats injected in the same way with 200 mg. per kg. body-weight were killed 4 at the first hour, and 6 at the second and third hours; 20 rats injected in the same way with 100 mg. per kg. body-weight were killed in groups of 4 at the first, second, third, fourth, and sixth hours; 20 rats injected in the same way with 50 mg. per kg. body-weight were killed at the first, second, third, fourth, and sixth hours; and 20 rats injected in the same way with 25 mg. per kg. body-weight were killed at the first, second, third, fourth, and sixth hours after the injection.

The number of circulating eosinophils, the amounts of ascorbic acid and cholesterol in the adrenals, the blood-salicylate level, and the histology of the adrenals, lymph-nodes, spleen, and thymus were studied in each rat as in the first group of experiments.

Results

Our results are summarised in figs. 5–8.

Fig. 5 shows that a decrease of 75% of the initial number of *circulating eosinophils* was observed after an injection of sodium salicylate 300 mg. per kg. body-

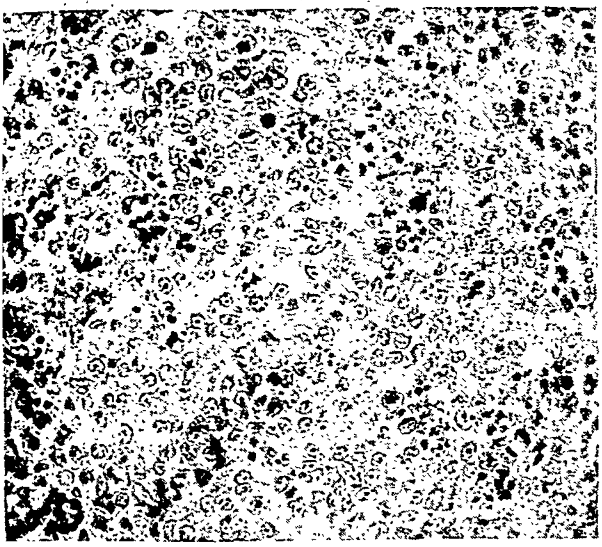


Fig. 4—Section of lymph-node showing numerous nuclear pyknoses 4 hours after injection with sodium salicylate 500 mg. per kg. body-weight in rat anæsthetised with dial (× 400).

weight. A decrease exceeding 60% was seen after the injection of 200 mg. per kg. No significant decrease was noted after the injection of sodium salicylate 100, 50, and 25 mg. per kg.

Fig. 6 shows that the injection of sodium salicylate 300 mg. per kg. body-weight produced a decrease of more than 50% of the amount of *ascorbic acid* in the adrenals. After 200 mg. per kg. there was a decrease of more than 30%; and after 100 mg. per kg. a decrease of 27% was observed at the third hour. There was no significant change of the amount of ascorbic acid in the adrenals after 50 and 25 mg. per kg.

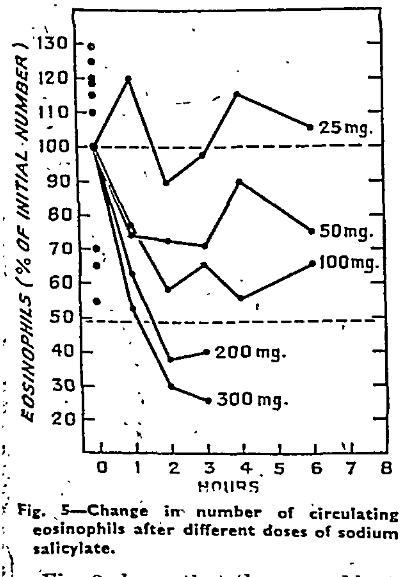


Fig. 5—Change in number of circulating eosinophils after different doses of sodium salicylate.

Fig. 7 shows that the amount of *cholesterol* in the adrenals decreased more than 65% after an injection of sodium salicylate 300 mg. per kg. body-weight; 60% after an injection of 200 mg. per kg.; 50% after one of 100 mg. per kg.; and 38% after one of 50 mg. per kg.; and there was no significant change after one of 25 mg. per kg.

Fig. 8 shows that the mean blood-salicylate level was directly related to the dose of salicylate administered intraperitoneally. Signs of adrenal activity were seen also after an intraperitoneal injection of 200, 100, and 50 mg. per kg. body-weight, though the blood-salicylate level was less than 30 mg. per 100 ml.

Histologically the decrease of the lipid content of the adrenals was greatest three hours after the injection of sodium salicylate 200 or 300 mg. per kg. body-weight. The histological signs are not constant after an injection of 100 mg. per kg., and no depletion was observed after an injection of 50 or 25 mg. per kg.

Nuclear pyknosis was common in lymphoid tissue after the injection of sodium salicylate 300, 200, and 100 mg. per kg. body-weight. The nuclear lesions were less numerous after an injection of 50 mg. per kg.; they were scarce after an injection of 25 mg. per kg. but were still to be seen in the lymph follicles (fig. 9).

Conclusion

When the doses of sodium salicylate injected intraperitoneally are progressively reduced, a gradual decrease of the adrenals' response is seen, some of the classical signs of their activity disappearing while others remain.

DISCUSSION

In normal animals the injection of a single high dose (500 mg. per kg. body-weight) of an isotonic sodium-salicylate solution produces a significant decrease in the number of circulating eosinophils and in the amount of ascorbic acid and cholesterol in the adrenals, and histological signs of adrenal hyperactivity (nuclear pyknosis in the spleen, lymph-nodes, and thymus) appear (Van Cauwenberge and Heusghem 1951b, Betz and Van Cauwenberge 1951).

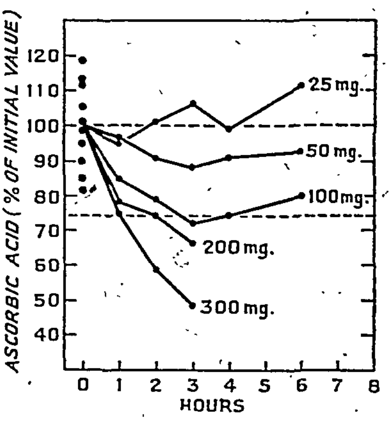


Fig. 6—Changes in amount of ascorbic acid in adrenals after different doses of sodium salicylate.

These changes are not seen in non-injected animals though they have been handled as for injection; nor are they seen in those injected with physiological saline solution or in hypophysectomised or adrenalectomised animals. Therefore we conclude that salicylates stimulate the adrenals through the pituitary (Van Cauwenberge 1951, Betz and Van Cauwenberge 1951).

As the biochemical and hæmatological signs of adrenal hyperactivity are suppressed or significantly decreased after a salicylate injection in dial-anæsthetised rats, and as dial, like other barbiturates, exerts a selective action on the hypothalamic-centre, we conclude that salicylates act in rats through a neuro-endocrine mechanism with a hypothalamic relay.

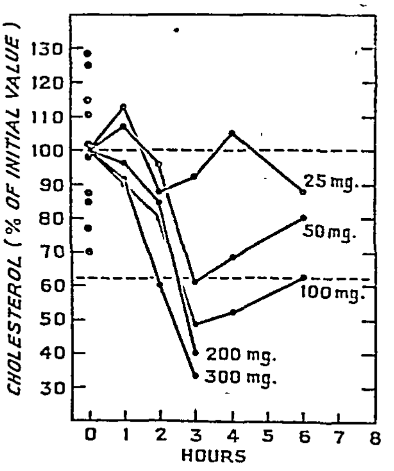


Fig. 7—Change in amounts of cholesterol in adrenals after different doses of sodium salicylate.

The presence of nuclear pyknosis in the lymphoid tissue of dial-anæsthetised rats injected with a single large dose of sodium salicylate, and, particularly, the effects of small doses of the drug, have shown us a gradient of responses among the various tests of activity of the pituitary-adrenal axis: circulating eosinophils were the least sensitive; ascorbic acid, cholesterol, and nuclear pyknosis followed, in that order. For instance, after an injection of sodium salicylate 100 mg. per kg. body-weight, the amount of ascorbic acid and cholesterol in the adrenals decreased and nuclear pyknosis appeared, but there was no significant change in the number of circulating eosinophils. After an injection of 50 mg. per kg., the amount of ascorbic acid did not decrease, but that of cholesterol did, and pyknosis appeared. After an injection of 25 mg. per kg., pyknosis was the only evidence of activity of the pituitary-adrenal axis. It must be emphasised that nuclear pyknosis is produced by an adrenal action, for it does not occur in adrenalectomised animals, even when a large dose of salicylate is injected.

Thus, independently of the changes which might occur through the handling of the rats, the intraperitoneal injection of a small dose of sodium salicylate stimulated the adrenals—the evidence for this being nuclear pyknosis in lymphoid tissue. Kelemen et al. (1950), studying the effect of sodium salicylate on the circulating eosinophils, did not observe a significant decrease in the number of circulating eosinophils when they injected into rats doses smaller than 300 mg. per kg. body-weight; but these workers have not described the conditions of their experiments.

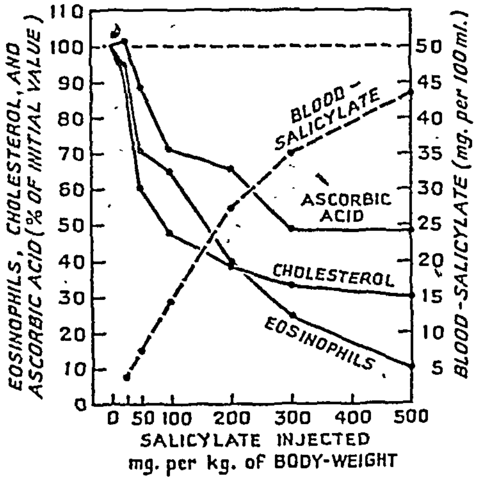


Fig. 8—Changes in blood-salicylate level, amounts of cholesterol and ascorbic acid in adrenals, and number of circulating eosinophils in relation to dose of sodium salicylate.

Hetzel and Hine (1951) found that even an injection of sodium salicylate 50 mg. per kg. body-weight depleted the amount of ascorbic acid in the adrenals, but they used a hypertonic solution (personal communication) and the rats were injected on several days.

Our observations seem much more conclusive. They helped us to understand the dissociation of the biochemical, hæmatological, and histological signs of activity of the pituitary-adrenal axis under dial anæsthesia.

No difference in response was observed between dial-anæsthetised rats given sodium salicylate 500 mg. per kg. body-weight and normal rats given 50 mg. per kg. Dial therefore seems to inhibit the adrenal response to salicylates. As barbiturates exert their effects principally on the hypothalamus (Fulton 1949), this inhibition suggests that the action of the salicylates is exerted on the hypothalamus.

CONCLUSIONS

(1) Signs of adrenal activity are produced by a dose of sodium salicylate smaller than that which produces the high blood-salicylate level regarded by Coburn (1943) as necessary for the treatment of acute rheumatism. Low blood-salicylate levels (6 or 7 mg. per 100 ml.) cause nuclear pyknosis in the lymphoid tissue of rats.

(2) Injection of sodium salicylate reveals a gradient among the responses generally regarded as evidence of adrenal stimulation.

(3) The response to injection of sodium salicylate is smaller in rats anæsthetised with dial.

(4) Inhibition of the pituitary-adrenal mechanism by barbiturates may be important in the treatment of certain endocrine disorders.

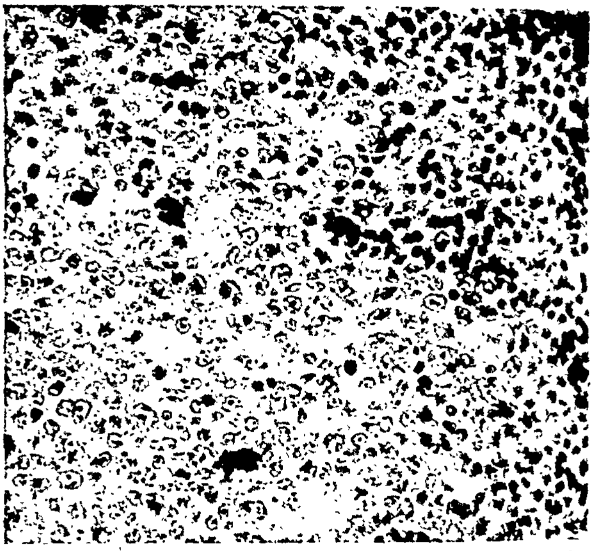


Fig. 9—Section of lymph-node showing nuclear pyknoses 4 hours after injection with sodium salicylate 25 mg. per kg. body-weight in non-anæsthetised rat.

(5) In the treatment of rheumatic disease it seems inadvisable to administer salicylates and large doses of barbiturates together.

We are indebted to the Belgian Foundation for Scientific Research for grants in aid of this investigation.

REFERENCES

Betz, H., Van Cauwenberge, H. (1951) *C.R. Soc. Biol. Paris,* 145, 1275, 1439.
Champy, C., Demay, M. (1951) *Bull. Acad. Méd. Paris,* 135, 13.
Coburn, A. F. (1943) *Bull. Johns Hopk. Hosp.* 73, 435.
Fulton, J. F. (1949) Textbook of Physiology. 16th ed., Philadelphia and London; p. 239.
Harris, G. W. (1950) Abstr. *Int. physiol. Congr.* p. 247.
Hetzel, B. S., Hine, D. (1951) *Lancet,* ii, 94.
Hume, D. W. J. (1949) *J. clin. Invest.* 28, 790.
Kelemen, E., Majoros, M., Ivanyi, J., Kovacs, K. (1950) *Experientia,* 6, 435.
Robinson, F. B. (1951) *Brit. med. J.* i, 300.
Roskam, J., Van Cauwenberge, H., Mutsers, A. (1951) *Lancet,* ii, 375.
Van Cauwenberge, H. (1951) *Ibid,* 374, 686.
— Heusghem, C. (1951a) *Ibid,* i, 771.
— — (1951b) *C.R. Soc. Biol. Paris,* 145, 1272.
— — (1952) *Acta med. scand.* 141, 265.

THE LATE PROGNOSIS IN ACUTE TUBULAR NECROSIS

AN INTERIM FOLLOW-UP REPORT ON 14 PATIENTS

K. G. Lowe
M.D. St. And., M.R.C.P.

LATE MEDICAL REGISTRAR AND TUTOR IN MEDICINE,
POSTGRADUATE MEDICAL SCHOOL OF LONDON

"Acute tubular necrosis" is synonymous with Lucké's (1946) term of "lower-nephron nephrosis" and includes a wide group of anurias following such varied causes as ingested poisons, mismatched blood-transfusion, abortion, and concealed accidental hæmorrhage. This group of anurias has probably always been of common occurrence, but it is only in the last decade or so that it has been adequately described and clearly recognised as a clinical and pathological entity. The extensive literature that has accumulated on the subject deals only with the acute episode of renal failure. As Burch and Ray (1949) point out, no adequate long-term follow-up of a series of cases has yet been reported.

Marshall and Hoffman (1949) showed that in 3 patients complete functional restitution of the kidneys to normal occurred, taking three months in 1 patient and nearly seven months in the other 2 patients. In a 4th patient considerable renal insufficiency persisted at the fourth month. Sirota (1949) studied 4 cases of acute tubular necrosis due to carbon tetrachloride poisoning. Though renal function usually returned to the lower limit of normal, the pattern of renal function in the post-convalescence phase suggested to him that there was some residual vascular damage. Burwell et al. (1947) report a case that came to necropsy three months after an episode of renal failure following abortion, death being due to homologous serum jaundice that supervened after a good clinical recovery had been made from the earlier illness. In this patient the urea clearance had not risen above 30% of normal three months after the acute episode. At necropsy the kidneys showed minor but definite changes, including subcapsular scarring, lymphocytic foci, and some dilated tubules with flattened epithelium and containing casts and desquamated epithelium. In view of the uncertainty about the late prognosis in such patients it was desirable that some attempt should be made at long-term follow-up, especially since so many of the patients seen in civilian practice are women in the childbearing era, and the question of advising in favour of, or against, future pregnancy often arises.

MATERIAL

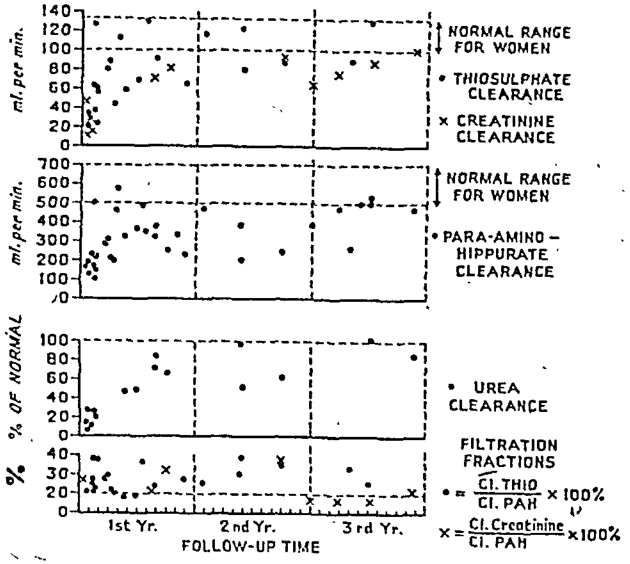
40 patients have been treated in Hammersmith Hospital since 1947 for anuria or severe oliguria due to tubular necrosis and 26 have recovered. A report on this series is in preparation (Bull, Joekes, and Lowe). Nearly all the patients were referred from other hospitals and, of the 26 who recovered, only 14 could attend for outpatient follow-up. The accompanying table gives relevant data about these patients. All had had severe episodes of renal failure, with periods of anuria or oliguria lasting from one to three weeks and peak blood-urea levels of 300–500 mg. per 100 ml. The pattern of disturbed renal function in these patients was studied and has been previously reported (Bull et al. 1950). There was no history of any other acute illness before or after the episode of acute tubular necrosis that would be likely to lead to renal damage.

RESULTS

In general, all the patients made a good clinical recovery from their acute illness and subsequently enjoyed good health. Without exception they had returned to their previous employment or to full household duties. Case 4 (see table) had an uneventful pregnancy three years

DATA RECORDED IN ROUTINE OUTPATIENT FOLLOW-UP OF 14 PATIENTS WHO HAD RECOVERED FROM ACUTE TUBULAR NECROSIS

Case no.	Age (yr)	Sex	Type of acute tubular necrosis	Days after onset of illness	Blood-pressure (mm. Hg)	Maximal concentration of urine (sp. gr.)	Urea clearance (% of normal)	Effective renal plasma flow	Glomerular filtration-rate		Filtration fractions		Remarks
								Para-amino-hippurate clearance (ml. per min.)	Thiosulphate clearance (ml. per min.)	Creatinine clearance (ml. per min.)	$\frac{\text{Cl. Thio.}}{\text{Cl. PAH}} \times 100\%$	$\frac{\text{Cl. Creatinine}}{\text{Cl. PAH}} \times 100\%$	
1	38	F	Post-abortion	37	..	..	..	172	37·2	..	21·6%	..	Good health
				76	..	..	..	287	80·5	..	28·0%	..	
				511	158/104	..	52·0%	204	80·0	..	39·5%	..	
				1127	155/95	..	..	..	..	..	..	..	
2	27	F	,,	95	..	..	..	215	..	..	..	..	Good health; occasional mild morning headache
				304	112/80	1·030	..	334	..	..	..	..	
				886	140/98	..	..	497	..	..	..	..	
3	24	F	,,	44	..	..	..	160	61	..	38·4%	..	Good health. Mild transient polyarthritis in first year of follow-up
				84	..	..	..	302	89	..	29·2%	..	
				192	130/94	1·028	..	494	..	..	..	..	
				815	..	..	..	475	..	76·5	..	16·2%	
4	27	F	,,	45	..	..	..	100	23	..	22·6%	..	Good health; subsequent normal pregnancy and delivery
				100	150/90	..	..	208	43·5	..	21·7%	..	
				731	..	..	..	388	..	65·3	..	16·9%	
				847	105/70	..	..	..	..	..	..	..	
				998	120/70	..	..	..	..	..	..	..	
5	24	F	Hæmolytic transfusion reaction	32	..	1·013	..	..	..	..	..	..	Good health; required treatment for iron-deficiency anæmia
				38	..	..	..	508	128	..	25·2%	..	
				116	..	..	..	582	116	..	19·9%	..	
				325	126/90	..	..	237	66	..	28·2%	..	
				918	..	..	..	533	..	87	..	16·3%	
6	42	F	,,	48	..	..	..	224	59·4	..	38·0%	..	Good general health since illness, but mild recurrent pains in finger-joints and aches in legs; severe episode of atypical pneumonia in 3rd year
				110	130/80	..	..	468	..	..	..	..	
				271	130/90	..	66·0%	254	..	82·3	..	32·4%	
				851	135/82	..	..	266	90	..	33·8%	..	
7	23	F	,,	506	124/88	..	99·0%	390	124	74·8	31·5%	19·2%	Occasional mild premenstrual headache since her illness
8	41	F	,,	232	140/96	..	84·0%	381	91·3	..	24·0%	..	Infrequent mild headaches since illness
9	38	F	Unexplained episode of intravascular hæmolysis following delivery of anencephalic monster	228	135/80	..	72·5%	332	..	71·3	..	21·5%	Good health
10	30	F	Anuria, following concealed accidental hæmorrhage	392	140/90	..	..	475	118	..	25·6%	..	Good health
				1052	135/95	..	86·5%	474	..	99	..	20·9%	
11	21	F	Mercury poisoning	29	..	..	..	136	..	..	..	..	Good health
				89	..	1·018	..	..	..	..	..	..	
				176	..	..	49·0%	376	70	..	18·8%	..	
				916	130/85	..	103·0%	505	131	..	25·9%	..	
12	39	F	Posthæmorrhagic shock	40	..	..	..	230	61	..	26·7%	..	Good health
				137	124/90	..	47·3%	326	59·5	..	18·1%	..	
13	19	F	,,	201	112/80	..	..	355	132	..	37·0%	..	Good health; nocturia (1x) since illness
14	51	F	? Myanesin poisoning	643	130/90	..	63·5%	248	88·5	90·8	35·7%	36·6%	Good health



Data of renal function during routine follow-up, in the outpatient clinic, of 14 patients who had survived severe episodes of acute tubular necrosis. A few of the clearances in the acute phase of the illness are also included to illustrate the pattern of recovery of renal function.

after her episode of renal failure. 3 patients had mild attacks of polyarthritis in their first year of follow-up, and 1 of these had a severe attack of "atypical pneumonia" later. Minor symptoms were mild headaches and, in 1 patient, nocturia. There were no noteworthy findings on physical examination except that some of the random blood-pressures were above the normal range. The significance of this was difficult to assess, because the circumstances of outpatient attendance were not such as to provide basal conditions.

Renal-function tests were made as convenient. Technical methods were as described elsewhere (Bull et al. 1950), except that the urine was not collected with a catheter. Since this may reduce the accuracy of these tests, they are presented not as exact indices of renal hæmodynamics but as simple tests of renal function. The accompanying figure and the table show that there usually is good recovery of renal function within the first *six months, and that this is sustained subsequently.* Renal function, however, tends to remain below the lower limit of normal. *In no case was there persistent* albuminuria or pathological deposit microscopically.

DISCUSSION

This follow-up report seems to indicate that, once recovery has been made from the acute episode of acute tubular necrosis, a favourable prognosis can be given. A lengthy convalescence of from three to six months may be advisable, because this is the time taken for renal function to approach the lower limit of normal, although physical well-being returns much more quickly. The slightly subnormal renal function in the late follow-up period is of interest. It may well be due to residua of the acute episode (scarring, vascular damage, &c.), but this remains open to speculation. At any rate, the levels of renal function attained are compatible with normal expectation of life, although the renal reserve is diminished. The occasional random blood-pressure readings outside normal limits invite speculation about whether hypertension will occur with undue frequency among such patients, but a follow-up of more patients and for a much longer time is required to answer this question.

This unit's policy was to allow subsequent pregnancies in these patients. As already stated, 1 patient was observed during and after a *normal pregnancy,* and, of the other patients who recovered but were unable to attend as outpatients, 2 had subsequent normal pregnancies.

SUMMARY

There has previously been doubt about the degree of recovery from acute tubular necrosis, and no previous long-term follow-up has been reported.

An interim follow-up report on 14 patients, some of whom have been seen for three years, is presented.

Good clinical recovery, which is sustained, is the rule.

The question of increased frequency of hypertension remains open.

Renal function becomes adequate but tends to remain below the lower limit of normal.

Pregnancy seems to be well tolerated subsequently.

Further follow-up of more patients and for a much longer time is required.

I am indebted to Dr. G. M. Bull for the opportunity to study patients under his care, and to Miss Barbara Evans, B.SC., for technical assistance.

REFERENCES

Bull, G. M., Joekes, A. M., Lowe, K. G. (1950) *Clin. Sci.* 9, 379.
Burch, G. E., Ray, C. T. (1949) *Ann. intern. Med.* 31, 750.
Burwell, E. L., Kinney, T. D., Finch, C. A. (1947) *New Engl. J. Med.* 237, 657.
Lucké, B. (1946) *Milit. Surg.* 99, 371.
Marshall, D., Hoffman, W. S. (1949) *J. Lab. clin. Med.* 34, 31.
Sirota, J. H. (1949) *J. clin. Invest.* 28, 1412.

WEIL'S DISEASE

A CAUTIONARY TALE

P. J. O'Connell
M.D. Durh., B.Hy., D.P.H.
MEDICAL OFFICER OF HEALTH, BOROUGH OF BEDDINGTON AND WALLINGTON

J. C. Broom
M.D. St. And.
BACTERIOLOGIST, WELLCOME RESEARCH INSTITUTION, LONDON

This investigation was undertaken as the result of a rash opinion expressed by one of us (J. C. B.), and because, at first, the mistaken diagnosis seemed to be confirmed by our inquiries. The error became apparent when more information was obtained, but we *think* that our findings have an intrinsic interest in addition to the warning they give against "spot diagnosis."

INTRODUCTION

In the early stages of leptospirosis a patient's *serum not infrequently reacts with more than one species* of leptospire; indeed Gispen and Schüffner (1939) found *that the titre against the infecting species might* be lower than the titre for some related serological type. Of less *common occurrence* is what Fühner (1951) calls the "paradoxical reaction," in which antibodies for a heterologous species appear, sometimes in high concentration, before any positive reaction can be demonstrated with the homologous leptospire. As the disease progresses the antibody level for the causal organism usually rises, while the titres for the heterologous species fall. But heterologous titres may remain at a high level until well into convalescence or even after recovery, and in such cases the diagnosis can be established *only* with the help of cross-absorption tests.

At the beginning of an illness, therefore, it *may be* possible to state only that the patient is suffering from leptospirosis. Thus, any device *is useful if it leads to* an early, complete *diagnosis,* because identification of the species is not *merely of academic interest.* If, for example, the causal organism is *Leptospira canicola,* the dog which was the source *of infection* may transmit the disease to other humans unless it is traced and rendered innocuous.

SEROLOGICAL INVESTIGATION

A boy, aged 15, fell ill on Aug. 8, 1951, and was thought by his doctor to be suffering from meningitis

He was admitted to hospital on the 10th, but the diagnosis was changed to non-paralytic poliomyelitis on the 15th.

Symptoms suggestive of meningitis or poliomyelitis have often been noted in both canicola fever and Weil's disease. Alston and Broom (1949) pointed out that the meningeal form of leptospirosis may closely resemble mild poliomyelitis without paralysis, and Chesney (1951) described how a typical case of canicola fever was at first mistakenly diagnosed in this way.

In the present case leptospirosis was not suspected until, at a late stage, the patient's condition grew worse and signs of gastro-intestinal disturbance developed with vomiting and jaundice. For this reason no agglutination test was made before the fourth week of the illness, when the serum was found to react with both *L. icterohæmorrhagiæ* and *L. canicola* to a titre of 1/300. With *L. canicola* the reaction was florid, whereas with *L. icterohæmorrhagiæ* the agglutination was not complete at any dilution of serum.

During the fourth week of the disease one normally expects a much higher titre than 1/300, but Broom (1951) refers to a few cases in which no antibodies could be detected until after the third week. In addition, the co-agglutination suggested present infection rather than a residual titre from a previous attack, so a diagnosis of leptospirosis seemed justified.

The type of reaction shown by the patient's serum had been observed from time to time, and the impression had been formed that the species which produced florid agglutination proved later to be the causal organism. With regrettable lack of caution, therefore, the patient's illness was pronounced to be canicola fever, and the search for an infected dog began.

The family dog had not been ill recently; but it might have been a healthy carrier, and specimens of blood and urine were therefore examined. The serum agglutinated *L. canicola* to a titre of 1/1000, and the urine to 1/100; both showed traces of agglutination with *L. icterohæmorrhagiæ* in dilutions of 1/10 only. Because the urine had been stored for some days before it was sent for investigation, no attempt was made to isolate a strain of leptospires by animal inoculation.

The high antibody concentration indicated either present or recent infection with *L. canicola*, and seemed to increase the likelihood of canicola fever. However, when a second specimen of the boy's blood was tested, the picture was completely altered. The serum titre was unchanged for *L. canicola*, but had risen for *L. icterohæmorrhagiæ*, and cross-absorption tests made it quite clear that the latter was the cause of the infection. A later blood sample confirmed the diagnosis of true Weil's disease (tables I and II).

EPIDEMIOLOGICAL INVESTIGATION

The patient lives in a house near the gates of a large factory. A tributary of the Thames skirts the whole length of the factory, and the river banks are easily reached from the house. Rats have infested the factory for many years, and a continuous campaign has been waged against them by the local authority and by the owners. In spite of this, people in nearby houses continually complain of invasion by rats, particularly during the summer.

TABLE I—AGGLUTINATION REACTIONS AT DIFFERENT STAGES OF ILLNESS

Weeks after onset of symptoms	Reciprocal of titre against	
	L. icterohæmorrhagiæ	*L. canicola*
4	300 (partial)	300
5	1000	300
6	10,000	30

TABLE II—AGGLUTINATION REACTIONS AFTER CROSS-ABSORPTION

5-week sample absorbed with	Reciprocal of titre against	
	L. icterohæmorrhagiæ	*L. canicola*
L. icterohæmorrhagiæ ..	0	0
L. canicola	1000	0

0 = negative at serum dilution of 1/30.

Before the boy fell ill, rats had raided the chicken-houses of one of his neighbours, and he had helped to repair the defences against them. He had worked in soft wet mud, which could easily have been infected, because some large dead rats were found near the chicken-houses.

A number of rats were trapped and examined. Traps set on three occasions caught 15 rats (*Rattus norvegicus*)—6 adult, 1 medium-sized, and 8 young. Dark-field microscopy revealed no leptospires in wet preparations of the kidneys of any of the rats in the first two batches. Hamsters inoculated with a pool of kidney tissue of the rats in the first batch (1 adult and 7 young) remained alive and well, but a strain of leptospires was isolated from the pooled material of the second batch (2 adult and 1 young). Numerous leptospires were visible in the kidneys of the 3 adults in the last batch, and a strain was isolated from them in the same way. The strains were tested serologically and both proved to be *L. icterohæmorrhagiæ*.

Although the number of rats was small, our results bring out clearly the low infection-rate in young rats as compared with adults. By chance the material also illustrates the viability of leptospires after the death of the host. The last batch (3 adult and 1 medium-sized) were killed on a Friday morning and they remained in the cold-room, at a temperature of about 5°C, from Friday evening to Monday morning. Three days after death, therefore, many active leptospires were seen in the kidneys of 1 of the adults, and the strain was isolated by inoculation of kidney suspension into a hamster. Smaller numbers of leptospires were present in the other 2 adults, but the hamster inoculated from their pooled kidneys showed no signs of infection either during life or at necropsy three weeks later.

DISCUSSION

The patient is a keen swimmer, and during the school holidays he spent much time in the local indoor swimming-baths. The element of fatigue involved in this strenuous exercise strengthened the opinion, formed in the early stages of his illness, that he might be suffering from poliomyelitis. But he denied swimming in the local river, in the Thames, or in casual ponds, so it was unlikely that the leptospiral infection was contracted while bathing.

It seems reasonably certain therefore that this boy was infected from the contaminated mud in which he had been working. There were no other cases of Weil's disease in the district, in spite of the presence of a considerable number of carrier rats, so it would appear that the conditions under which the boy worked exposed him to special risk of infection. This is quite likely, because Alston and Brown (1937) noted that, among sewer-workers, Weil's disease is much less common in "flushers" who clean the sewer walls than in builders' labourers who handle broken brick-work covered with mud from the bottom of the sewer.

The infection of the dog with *L. canicola* would probably never have been suspected but for the original anomalous agglutination result. The coincidence is interesting, but not inherently improbable, considering the large proportion of dogs infected with this species. For instance, Joshua and Broom (1949) found serological evidence of past infection in 45 out of 121 London dogs of all ages. One might expect therefore that, on the average, about one-third of the dogs belonging to patients suffering from Weil's disease had been affected at some time with canicola fever. The only unusual feature in this case is the high titre in the dog's serum, which indicates that the human and canine infections with different species were more or less concurrent.

SUMMARY

A boy aged 15 developed an illness which in the fourth week was shown to be leptospirosis. Agglutination reactions suggested canicola fever rather than Weil's disease, and the boy's dog showed evidence of recent infection by *L. canicola*. But later tests established the diagnosis as Weil's disease. The infection in the dog was fortuitous.

The boy had been working in wet mud which could easily have been contaminated with rats' urine. Rats caught near his home were found to carry *L. icterohæmorrhagiæ*.

This story illustrates the need for caution in diagnosis when a patient's serum reacts with more than one species of leptospire.

We should like to thank Dr. G. H. Hall, who provided us with clinical material and information, and Mr. R. J. Reed, who examined the rats and isolated the strains of leptospires.

REFERENCES

Alston, J. M., Broom, J. C. (1949) *Lancet*, ii, 306.
— Brown, H. C. (1937) *Proc. R. Soc. Med.* 30, 711.
Broom, J. C. (1951) *Brit. med. J.* ii, 689.
Chesney, G. (1951) *Mon. Bull. Min. Hlth*, 10, 78.
Fühner, F. (1951) *Z. ImmunForsch.* 108, 278.
Gispen, R., Schüffner, W. (1939) *Zbl. Bakt.* 144, 427.
Joshua, J. O., Broom, J. C. (1949) *Vet. Rec.* 61, 711.

PARACOLON BACILLUS SEPTICÆMIA

R. J. Kernohan
M.D. Belf., M.R.C.P., M.R.C.P.I., D.P.H., D.C.H.
PHYSICIAN, MID-ANTRIM HOSPITAL GROUP

SEPTICÆMIA caused by organisms of the paracolon group is very rare. In the following case, which presented as one of severe septicæmia, after initial dysenteric symptoms, complete recovery followed chloramphenicol therapy.

CASE-RECORD

A girl, aged 4 years, had had an uncomplicated attack of measles three weeks before admission. Three days before admission she complained of lower abdominal pain and malaise. Her temperature was then 101°F, and she passed several loose stools containing mucus and a slight amount of bright-red blood.

Condition on Admission.—She was a well-nourished child with a malar flush. The temperature was 103°F, and the pulse-rate 110 per min., soft and regular. She was somewhat drowsy and very listless. Her throat was mildly injected, and her tongue coated with whitish fur. There was tenderness in the right iliac fossa, but no guarding or rigidity. No other abnormal physical signs were elicited. The urine contained no abnormal constituents, and a catheter specimen revealed no pus cells and was sterile on culture. A Mantoux test was negative. Lumbar puncture shortly after admission yielded clear colourless cerebrospinal fluid under normal pressure. Examination of the peripheral blood showed Hb 90%, erythrocytes 4,500,000 per c.mm., and leucocytes 5700 per c.mm. (polymorphs 68%, lymphocytes 25%, mononuclears 5%, eosinophils 2%).

Progress.—Two days after admission there was little change in the child's clinical condition. Her abdomen was slightly distended, but there was now no tenderness. She had passed three loose stools per day, the fæces containing neither blood nor mucus. At this stage the clinical picture suggested enteric fever. A gram-negative rod-shaped bacillus, which was culturally and biochemically a paracolon bacillus, was isolated from specimens of both blood and fæces taken on the second day. Treatment with chloramphenicol was started on the fourth day after admission in a dosage of 2 g. at once followed by 0·5 g. six-hourly. The child's condition continued to deteriorate, and on the fifth day she was gravely ill and toxic, her pulse being rapid and feeble, and respirations shallow. She lapsed into semi-coma. Intravenous glucose-saline solution and plasma were administered. Chloramphenicol was continued in the same dosage. After a further two days there was a considerable improvement. Bacteriological examination of the fæces and blood-culture on the seventh day again revealed a paracolon bacillus. After this day repeated bacteriological examinations of the blood and fæces were negative. Chloramphenicol was continued for a further seven days in the dosage of 0·25 g. six-hourly. The total dose administered was 18 g. in eleven days.

Improvement was maintained, and the child was discharged from hospital four weeks after admission. No complications developed during convalescence, and she remains well.

DISCUSSION

The paracolon bacillus (*Bacterium paracoli*) was recognised as a distinct organism by Mair in 1906. He found it associated with acute infections of the urinary tract. However, general acceptance of it as a separate organism has been recent. It is gram-negative, seldom motile, and rod-shaped, with colonies resembling those of *Bact. coli* in form, but dirty white, with a suggestion of pink in the centre on McConkey's agar medium. It is regarded as an intermediate between *Bact. coli* and the paratyphoid group, and differs culturally from *Bact. coli* in that it ferments lactose slowly, poorly, or not at all. It differs biochemically from the paratyphoid group in that it gives a positive indole reaction, and it also does not agglutinate with paratyphoid-agglutinating serums.

In the past few years several reports have appeared on cases of gastro-intestinal infection and outbreaks of colitis due to organisms of the paracolon group which have responded to streptomycin therapy (Block et al. 1949, Dornall 1948). These organisms have generally been regarded as being of low pathogenicity (Wilson and Miles 1946).

There have also been reports of recovery of paracolon bacilli from the blood-stream, the earliest being that of Dudgeon and Pulvertaft (1927). They were working with late-lactose-fermenting organisms isolated from the urine of patients with unusually severe pyelitis. De Assis (1927) isolated from the blood-stream an organism which he named *Proteus pseudovalericæ* but which Rustigian and Stuart (1943) pointed out should be classified as a paracolobactrum. The number of reports of isolation from the blood-stream is not large. However, Block et al. (1949), reporting a case of acute dysentery caused by a paracolon escherichia (Breed 1948), mention that Wheeler has isolated paracolon bacilli on several occasions from the blood-stream of typhoid-like cases, and that they themselves have studied three patients from whom they isolated paracolons from either blood or intestinal tract before death.

Other fatal cases of paracolon infections are those of Robertson (1947), who described endocarditis of the pulmonary valve, secondary to infected polycystic kidneys, in a man aged 40; of Friedman and Goldin (1949), whose case was that of a diabetic woman, aged 54, who had mitral endocarditis, the primary focus of infection being a pyelonephritic kidney; and of Walton and Leedham-Green (1947), who described a case which occurred after an attack of dysentery, and in which the somewhat rare sequels of acute cholecystitis and suppurative hepatitis developed, and *Bact. paracoli* was recovered from the blood-stream and from the gall-bladder during the infection and from the lesions in the liver at necropsy.

In the present case the isolation of the organism in pure culture from the fæces and blood, and the clinical picture, seemed to make it certain that this organism was the responsible ætiological agent. It is very difficult to explain the deterioration for the first forty-eight hours after the administration of chloramphenicol. The route of infection was gastro-intestinal. There was no evidence of involvement of the genito-urinary tract.

There is no doubt that *Bact. paracoli,* which has reputedly weak invasive powers, can on occasion produce profound toxæmia. The pathogenicity in such cases is due to lack of an adequate immunological response, which may be caused by the patient's debility or chronic illness. In the present case no definite explanation can be offered why the paracolon bacillus caused an almost overwhelming infection.

SUMMARY

A case of septicæmia due to *Bact. paracoli* in a child aged 4 years is described. Complete recovery followed treatment with chloramphenicol.

The pathogenic rôle of *Bact. paracoli* may not be so limited as previous reports suggest.

REFERENCES

Block, L., Milzer, A., Kerdeman, E. (1949) *Gastroenterology,* 12, 508.
Breed, R. S. (1948) Bergey's Manual of Determinative Bacteriology. London.
De Assis, A. (1927) *J. Hyg., Camb.* 27, 108.
Dornall, C. R. (1948) *Gastroenterology,* 10, 366.
Dudgeon. L. S., *J. Hyg., Camb.* 26, 385.
Friedman, I. A. *clin. Path,* 19, 840.
Mair, W. (1906)
Robertson, T.
Rustigian, R., *oc. Soc. exp. Biol., N.Y.* 53, 241.
Walton, K., Leedham-Green, J. C. (1947) *Brit. med. J.* ii, 1033.
Wilson, G. S., Miles, A. A. (1946) Topley and Wilson's Principles of Bacteriology and Immunity. London.

NEPHROTIC SYNDROME COMPLICATING TRIDIONE (TROXIDONE) THERAPY

J. D. N. Nabarro
M.D. Lond., M.R.C.P.
FIRST ASSISTANT IN THE MEDICAL UNIT

M. L. Rosenheim
M.D. Camb., F.R.C.P.
PROFESSOR OF MEDICINE IN THE UNIVERSITY OF LONDON; DIRECTOR OF THE MEDICAL UNIT

UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL, LONDON

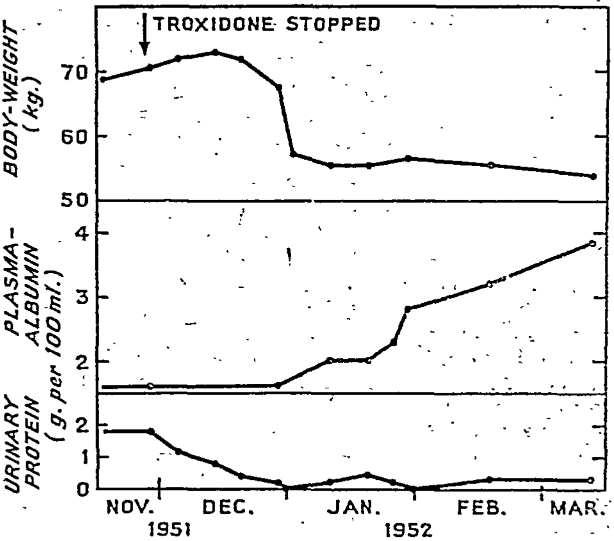
'Tridione' (troxidone *B.P.C.*) is of value in the management of cases of petit mal. A number of toxic effects may follow prolonged administration, and of these the most important and best known are aplastic anæmia and agranulocytosis. Disturbance of renal function producing a nephrotic syndrome, with severe albuminuria and hypoproteinæmic œdema, has been reported in a few patients. This complication is apparently rare, but it is important that the association should be recognised, and the following additional case is therefore described.

CASE-RECORD

A young married woman developed epilepsy in 1946 at the age of 19. Initially she was treated with phenobarbitone, but in 1949, when electro-encephalography showed a mixed pattern suggesting grand and petit mal, 'Epanutin' (phenytoin sodium *B.P.C.*) and troxidone were added. The dose of troxidone was 1·5 g. daily and this was continued without interruption. Blood-counts were performed from time to time and remained normal.

The patient was first seen at University College Hospital in 1950 for recently developed and incapacitating Raynaud's disease, for which various vasodilator drugs were tried and later bilateral cervical sympathectomy performed with some benefit.

The urine was examined on many occasions, and up to November, 1950, was free from albumin. In May, 1951, when the patient had been taking troxidone for 2 years (an approximate total of 850 g.), she first noticed œdema of the legs.



Changes in body-weight, plasma-albumin, and urinary protein after stopping troxidone.

She was readmitted to hospital in June, 1951, and the urine was found to contain protein (0·18 g. per 100 ml.) and occasional pus cells, the blood urea was 30 mg. per 100 ml., urea clearance and concentration tests were normal, and the plasma-albumin was 1·9 g. and plasma-globulin 2·1 g. per 100 ml. The blood-pressure was normal. Despite treatment with a low-sodium diet (300 mg. per day) the patient's weight rose steadily from 54 kg. in June to 70 kg. in November, and œdema became generalised. The proteinuria increased, reaching a maximum of 3·7 g. per 100 ml., the serum-albumin fell to 1·5 g. per 100 ml., and the electrophoretic pattern was characteristic of nephrosis.

At this time the report of Barnett et al. (1948) was noted and on Nov. 28 the troxidone was stopped. After four weeks there was a brisk diuresis and the weight and plasma-albumin returned to normal (see figure). The grand mal is now controlled by phenobarbitone alone, but petit mal is a little more frequent than during the troxidone period. The Raynaud's phenomenon was unaffected by stopping troxidone.

DISCUSSION

Barnett et al. (1948) described the case of a girl aged 14 who developed nephrosis after $8^1/_2$ months of troxidone therapy, but whose renal function returned to normal within a few weeks of stopping the drug. Treatment was resumed on two occasions, and each time the nephrosis recurred after 8 weeks. The causal relationship was well established in this patient. Briggs and Emery (1949) described a boy of 8 who developed nephrosis after 3 months' treatment (1·5 g. daily); there was no improvement when the drug was stopped for two periods of 6 and 5 weeks. It was restarted and given until the boy died 4 months later. A third patient (White 1949) developed nephrosis after 11 months' treatment with smaller doses (0·3 to 0·6 g. daily); diuresis occurred within 2 weeks of the drug being stopped. Our patient developed a typical nephrotic syndrome after 2 years' treatment. It progressed steadily until troxidone was stopped and then regressed rapidly, although a trace of protein is still present in the urine.

Wilson et al. (1952) have recently reported a series of typical cases of type II nephritis in children given mercurial teething-powders. It seems to be as important in nephritis as in hepatitis to inquire into the possibility of drugs as a cause.

REFERENCES

Barnett, H. L., Simons, D. J., Wells, R. E. (1948) *Amer. J. Med.* 4, 760.
Briggs, J. N., Emery, J. E. (1949) *Lancet,* i, 59.
White, J. C. (1949) *J. Amer. med. Ass.* 139, 376.
Wilson, V. K., Thomson, M. L., Holzel, A. (1952) *Brit. med. J.* i, 358.

THE EFFECT OF DIMERCAPROL ON HYPERTENSION

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JUNIOR LECTURER IN PATHOLOGY

R. Kauntze
M.B.E., M.D. Camb., F.R.C.P.
ASSISTANT PHYSICIAN
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We have injected dimercaprol intramuscularly in doses of 3–6 mg. per kg. body-weight into four patients with essential hypertension without producing any fall in blood-pressure during the two hours following injection (see table). On the contrary, the blood-pressure rose slightly or moderately with 3–4 mg. per kg. body-weight and alarmingly with 6 mg. per kg. The rise in blood-pressure usually began twenty to thirty minutes after injection and persisted for fifty to a hundred minutes. With intramuscular dimercaprol 6 mg. per kg. body-weight (see figure) the rise in blood-pressure was more extensive (from 225/145 to 265/185 mm. Hg), of shorter duration, and accompanied by increase of heart-rate.

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Case no.	Diagnosis	Age (yr.) and sex	Resting B.P. (mm. Hg)	Dimercaprol I.M. (mg. per kg. of body-weight)	After injection			Remarks
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2	Essential hypertension in malignant phase	47 M	250/150	3	275/160	No change	50–95	
3	Benign essential hypertension	48 M	225/145	6	265/185	+16	20–70	
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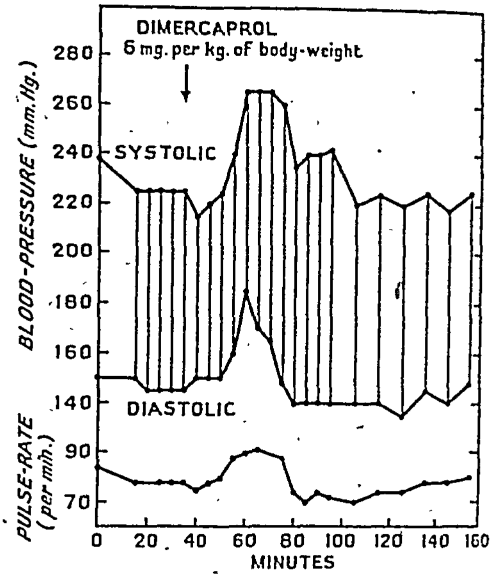

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THE FATE OF THE FACE IN POLIOMYELITIS

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This paper reviews 14 cases of facial paralysis in 13 patients (including 1 bilateral complete palsy) and the degree of recovery a year or more after the onset.

There were 5 patients under the age of five years, 6 between five and fifteen, and 2 over the age of fifteen. 10 of the 13 patients were admitted during the second half of the year. 11 had neck stiffness in the early part of their illness, and the cerebrospinal fluid findings in all of them were compatible with a diagnosis of poliomyelitis.

The 14 cases of facial paralysis were equally divided as regards side and comprised 8 involving upper and lower halves (complete paralysis) and 6 with weakness of the lower half only (partial paralysis). 5 of the 8 complete palsies and 4 of the 6 partial ones were associated with paralysis elsewhere.

When seen a year or more after the onset all the patients with partial paralysis had completely recovered from their facial paresis, without any specific treatment. Recovery had taken from a few weeks up to six months, the patients with the slightest paralysis recovering the most quickly.

On the other hand, 7 of the 8 complete facial palsies still showed some residual weakness, more apparent in the lower half of the face, a year or more after onset. A variable degree of recovery had taken place, mostly within the first six months. The exception was a boy of four years, whose complete facial paralysis had recovered completely within three months.

Agius et al. (1945) observed 47 cases of facial paralysis among 426 cases of poliomyelitis in the Malta epidemic of 1942–43; 10 of these still showed some residual facial weakness two years later. Rascoff (1949), in America, followed up 23 cases of facial paralysis considered to be due to poliomyelitis, and after two years 11 showed some residual weakness. Rascoff commented that little or no recovery took place after a year. These workers do not mention any association between the degree of recovery and the extent of the paralysis at onset.

The view is sometimes expressed that complete recovery from cranial-nerve palsies in poliomyelitis may be expected, provided that the acute phase of the disease is survived. From the results of the two series cited above and from the present investigation it appears that facial paralysis does not conform to this view. Indeed, the pattern of recovery is similar to that which obtains in paralysed muscles supplied by the spinal nerves—i.e., the degree and speed of recovery are related to the severity of paralysis. From the results in the present series it seems that one could be reasonably confident in predicting complete recovery from paralysis involving the lower part of the face only, but that prognosis should be more guarded where both upper and lower halves are affected.

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Preliminary Communication

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During the last two years seventeen children have been studied showing features common to those described by both Lignac and Fanconi, and in all of them cystine crystals were found in the bone-marrow. The fact that cystine is the least soluble amino-acid and the first to crystallise in the tissues has perhaps led to its receiving particular attention, though possibly there is a far more extensive disturbance of the amino-acid metabolism. Therefore the term "cystine storage disease" may prove to be an incomplete description and may have to be changed if the presence of excess of other amino-acids in the tissues is established as a characteristic of this disease.

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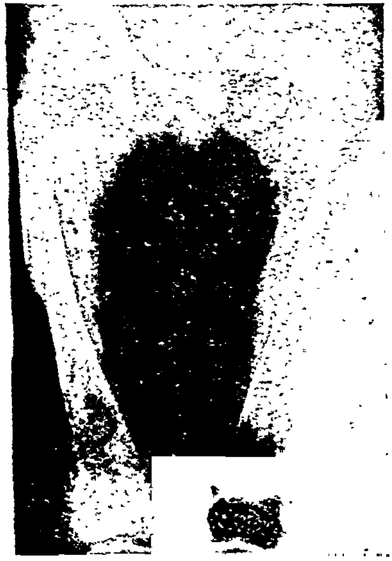
Fig. 1—Osteomalacia with moderate rickets in child aged 9 years, showing healed pathological fracture of right femur.

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Most of the patients did well for the first few months of life and then, often about weaning-time, began to vomit, to refuse food but to cry for drink, and to pass abnormal quantities of urine. They were brought to hospital owing to loss of weight, cessation of growth, or toxic crises with persistent vomiting. In children aged more than 2 years the course of the disease was generally less dramatic. Often the first and most striking symptom was rickets, resistant to ordinary therapeutic doses of vitamin D. Severe osteomalacia with pathological fractures had developed occasionally (fig. 1). Three patients, on the other hand, showed practically no bone changes. In the more chronic form of the disease medical advice may be sought for dwarfism, deformities, or tetanic or uræmic attacks. One patient was admitted as a suspected case of diabetes after the discovery of glycosuria.

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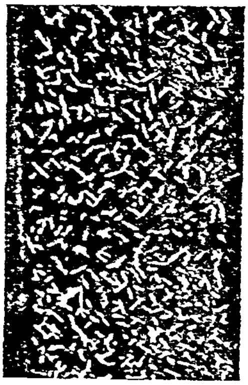
Fig. 2—Narrow beam of slit-lamp showing cystine crystals in cornea (drawing by Mr. A. A. Douglas).

Cystine crystals were demonstrated in the bone-marrow in all seventeen children (fig. 4). These crystals may be overlooked if they are scanty, and because they are soluble in water and acid stains. The most reliable method for their detection in vivo is microscopy of a lymph-gland, as has been demonstrated by Dr. H. S. Baar. The identity of the cystine in bone-marrow and lymph-gland was confirmed by paper chromatography.

The clinical picture is further characterised by sudden and unaccountable rises in temperature, vomiting, glycosuria, albuminuria, polyuria, hypophosphatæmia with normal urea, normal calcium, and normal or raised blood-phosphatase levels, and hypopotassæmia, which may be associated with changes in the electrocardiogram. Hypopotassæmia was found in all the five patients tested (with levels as low as 1·8 m.eq. per litre) and is probably responsible for some of the clinical symptoms—e.g., muscular weakness, vascular collapse, and glucose shocks. The alkali reserve is usually low, the ammonia coefficient in the urine is generally raised, and the urine often

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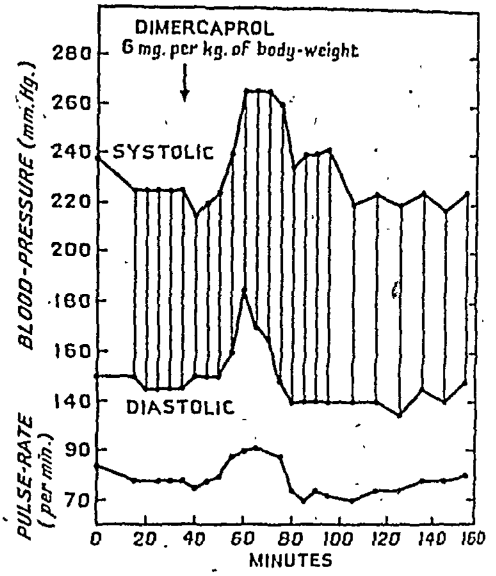

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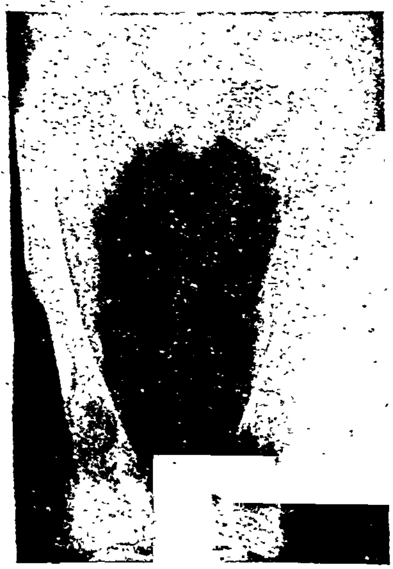

Fig. 1—Osteomalacia with moderate rickets in child aged 9 years, showing healed pathological fracture of right femur.

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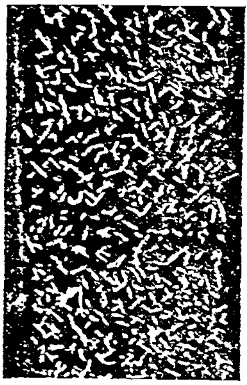

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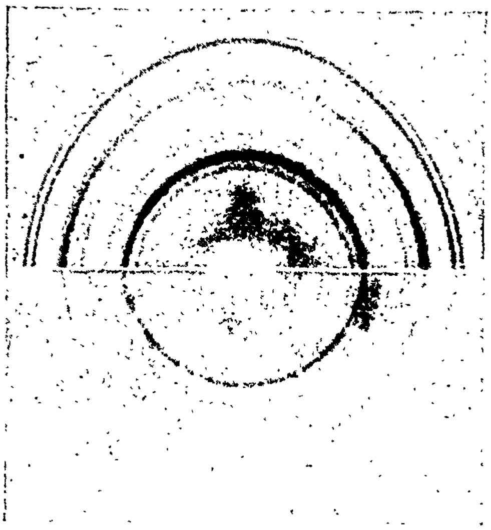

Fig. 3—X-ray diffraction rings: *above*, pure cystine; *below*, cystine in biopsy specimen of conjunctiva.

contains an abnormally large amount of bicarbonate. In the diagnosis it is important to note that any of these findings may be intermittently or completely absent; for example, the alkali reserve can occasionally be normal, even in severe cases, but always falls to very low values (below 20 vols. per 100 ml.) in the dangerous acidotic crises which clinically resemble diabetic coma. In three children the urine never gave a positive Benedict test, but chromatography did reveal pathological traces of glucose. Furthermore, raised blood-urea and blood-phosphorous levels were observed not only in the late stages but also temporarily early in the disease.

Amino-aciduria is a feature of special importance, and most of our patients were discovered by paper chromatography (Consden et al. 1944, Dent 1947, 1948, Hermann et al. 1949). This amino-aciduria, together with cystine storage, is pathognomonic. Cystine is only one of 10–20 amino-acids which are excreted in excess, and it may be no more important than the others (fig. 5). Compared with normal urine chromatograms the increase of valine, the leucines, phenylalanine, tyrosine, and proline was especially striking. The intensity of the amino-aciduria corresponds to the severity of the disease: it is very pronounced in the acute infantile form, but is slight, and may easily remain undetected, in the chronic form. In some cases it varies considerably from day to day; an occasional normal chromatogram showing no amino-aciduria does not, therefore, prove the absence of the disease, but in all suspected or doubtful cases the test must be repeated several times. In addition to amino-aciduria there is also a considerable increase in the amino-acid content of the blood-plasma. We are indebted to Prof. H. A. Krebs, F.R.S., of the University of Sheffield, and Dr. K. Schreier, of the University of Heidelberg, for making quantitative estimations of the plasma levels of various amino-acids. Microbiological assay has shown 50–100% increase of various amino-acids, and Professor Krebs found a similar increase in the plasma of glutamine and glutamic acid. This confirms the chromatographic finding of an increased plasma level for various amino-acids (Bickel, cited by Fanconi 1950).

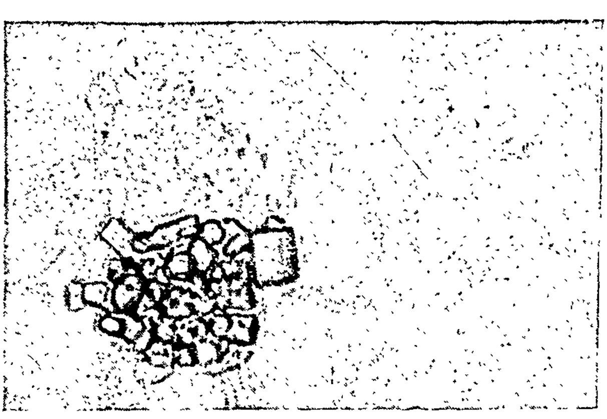

Fig. 4—Cystine crystals in bone-marrow.

THERAPY AND PROGNOSIS

Fanconi's (1950) review of the treatment of this metabolic disturbance is pessimistic. So far no case of cystine storage disease has been observed after puberty. In the acute form death takes place early, usually in a metabolic crisis with acidosis and probably hypopotassæmia (Drablos 1951). The later stages of the chronic form are characterised by progressive kidney damage, and the more advanced this damage the more remote are the possibilities of response to therapy.

In the care and management of our patients three measures have been considered important: (1) massive doses of vitamin D (up to 500,000 units daily, and later a maintenance dose of 10,000–30,000 units daily); (2) a mixture of sodium citrate, citric acid, and water (up to 20 g. of sodium citrate daily by mouth); and (3) potassium chloride 2 or 3 g. daily. The results have been most promising. The alkali reserve and potassium level in the blood return to normal and the rickets heals, and there is considerable clinical improvement. Further metabolic crises have not been observed, vomiting has ceased, and the children are livelier and stronger—three are now walking for the first time. Their appetite has improved, though gains in weight and height are still delayed. The most striking and perhaps prognostically the most important effect of alkalinisation (adequate to restore the plasma-alkali reserve to a normal level) has been the gradual reduction and eventual disappearance of amino-aciduria and glycosuria for at least six months.

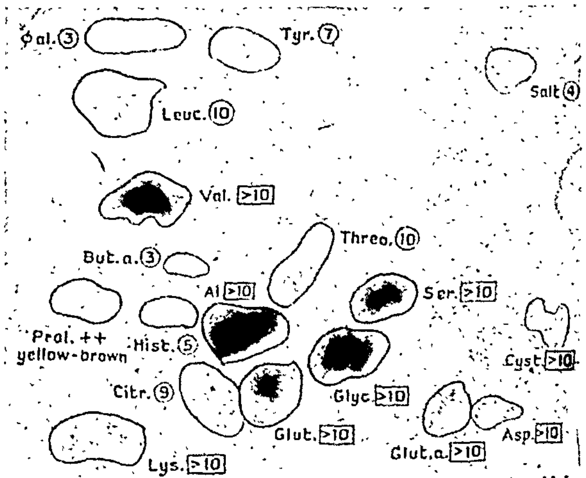

Fig. 5—Urine chromatogram showing general amino-aciduria. Urine volume = 500 µg. nitrogen. Al., alanine. Asp., aspartic acid. But.a., alpha-amino-n-butyric acid. Citr., citrulline. Cyst., cysteic acid from cystine. Glut., glutamine. Glut. a., glutamic acid. Glyc., glycine. Hist., histidine. Leuc., leucines (leucine and/or isoleucine). Lys., lysine. Prol., proline. Ser., serine. Threo., threonine. Tyr., tyrosine. Val., valine. φal., phenylalanine. Figures at side of amino-acid names indicate relative colour intensities of spots—1 for weakest, > 10 for strongest, colour.

SUMMARY

Seventeen children with cystine storage disease characterised by amino-aciduria have been investigated, and the results are given in brief.

Cystine storage was detected in all the cases in bone-marrow, in a lymph-gland biopsy, or by slit-lamp investi-

gation of cornea and conjunctiva. The diagnosis was further facilitated by the demonstration of 10–20 amino-acids in the urine by paper chromatography.

The plasma levels of various amino-acids were shown by microbiological, chemical, and chromatographic methods to be raised 50–100%.

The variability of nearly every symptom and sign is emphasised. X-ray evidence of rickets may be absent, the constitutional upset can remain slight for years, and glycosuria may be present in too minute amounts to be detected by the usual chemical tests. Blood-urea, blood-phosphorus, and blood-alkali reserve show similar variation.

Hypopotassæmia is deemed to be a factor of importance in the production of certain features of the disease.

Treatment with high vitamin-D dosage, potassium salts, and sodium citrate has given promising results.

These studies could not have been made without the sustained interest, advice, and constructive criticism of many colleagues in addition to those acknowledged in the text. We are grateful to these and to many others who gave so freely of their time, skill, and experience as well as to the physicians who allowed us to study their patients. Full acknowledgment will be made in the detailed papers which are being published shortly.

REFERENCES

Consden, R., Gordon, A. H., Martin, A. J. P. (1944) *Biochem. J.* 38, 224.
Drablcs, A. (1951) *Acta pædiatr. Stockh.* 40, 438.
Dent, C. E. (1947) *Biochem. J.* 41, 240.
— (1948) *Ibid*, 43, 169.
Fanconi, G. (1936) *Jb. Kinderheilk.* 147, 299.
— (1950) *Schweiz. med. Wschr.* 80, 757.
Hermann, F., Bickel, H., Fanconi, G. (1949) *Helv. pædiat. Acta*, 4, 397.
Lignac, G. O. E. (1924) *Dtsch. Arch. klin. Med.* 145, 139.
— (1926a) *Krankheitsforschung*, 2, 43.
— (1926b) *Verhdlsch. path. Ges.* 21, 303.

H. BICKEL
M.D. Vienna
Research Scholar

J. M. SMELLIE
O.B.E., T.D., M.D. Edin., F.R.C.P.
Professor of Pædiatrics and Child Health

Department of Pædiatrics and Child Health, University of Birmingham

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Reviews of Books

Text-Book of Ophthalmology

Vol. 5, *The Ocular Adnexa*. Sir STEWART DUKE-ELDER, K.C.V.O., M.D., D.SC., LL.D., F.R.C.S., F.A.C.S., consulting ophthalmic surgeon to the British Army and the Royal Air Force; Director of Research, Institute of Ophthalmology, University of London; consulting surgeon to Moorfields, Westminster and Central Eye Hospital, London. London: Henry Kimpton. 1952. Pp. 1082. 90*s*.

THIS is the penultimate volume of what has now become the most complete and all-embracing manual of ophthalmology ever written. Indeed, there is nothing like it today in any country in any branch of medicine or surgery; and with the publication of vol. 6 on injuries the series will be complete. Ophthalmologists will have read its predecessors and know how much they can expect of this volume; and they will not be disappointed. It deals with the lids, lacrimal apparatus, orbit, and para-orbital regions; and, beginning with developmental anomalies, it traces the disorders of circulation, inflammations, metabolic disorders, cysts, and tumours, and the motor and sensory disorders that affect those parts. The scope and sweep of the work leaves the reader amazed, for it touches on all branches of medicine. Sir Stewart Duke-Elder is at once dermatologist, geneticist, physiologist, rhinologist, and physician; and in each department he presents in lucid prose not only the salient facts but much important detail. His work leaves the medical profession deeply in his debt.

Modern Practice in Tuberculosis

Vols. 1 and 2. Editors: T. HOLMES SELLORS, M.A., D.M., F.R.C.S., thoracic surgeon, Middlesex Hospital; J. L. LIVINGSTONE, M.D., F.R.C.P., physician, King's College Hospital. London: Butterworth. 1952. Pp. 355 and 441. £7 7*s*. (for both volumes).

THE editors of this book "invited their contributors to submit their opinion on a variety of different subjects." The result is not a textbook but a collection of essays, each of which is necessarily coloured by the individual opinions of the author, nearly all of them admirable. The subject matter in the first volume is general—it opens with a delightful and thoughtful article on the epidemiological angle, by the late Dr. Roodhouse Gloyne. Pathogenesis, pathology, and bacteriology are all discussed in subsequent chapters, and those who support the endogenous origin of phthisis will welcome A. L. Jacobs's chapter on The Seed and the Soil. Diagnosis and general management, the value of fluorography, the assessment of the minimal lesion, rehabilitation, administrative aspects, and the place of modern drugs in treatment are included. Dr. H. J. Ustvedt of Oslo, who gives a lucid yet compressed account of the evidence in favour of B.C.G. vaccination, is the only foreign contributor. The dangers of omission inherent in multiple authorship have been largely avoided. Clinical diagnosis, however, has been heavily overlaid by radiology, and the effects of pregnancy and parturition have received less consideration than modern views demand.

The second volume of the work deals chiefly with pulmonary tuberculosis, but also has less detailed chapters on tuberculosis of other systems and organs, the ear and larynx excepted. It emphasises throughout that tuberculosis is a general disease, and should not be divided into watertight compartments, system by system. Acknowledged authorities have contributed chapters on the various types of collapse therapy, including phrenic crush, thoracoplasty, artificial pneumothorax, and pneumoperitoneum, and on resection, pleural effusion, tuberculous empyema, primary tuberculosis, tuberculous tracheobronchitis, sarcoid, and pericarditis, as well as tuberculosis of other systems. The book is liberally illustrated, and the many fine radiographs clarify points made in the text. It will serve as a valuable work of reference for many years to come.

L'hypertension artérielle permanente

Indications médicales des interventions neuro-endocriniennes. P. ÉTIENNE-MARTIN, professor of clinical medicine, Dijon School of Medicine. Paris: Doin. 1951. Pp. 269. Fr. 1850.

Professor Étienne-Martin has performed a notable service in bringing together, in the first half of his book, the published data concerning the evolution of hypertension, its complications, prognosis, and physiopathology, and in the second half the results of the various surgical treatments. The differing opinions and results have been weighed against his own extensive experience. The resulting work is a carefully balanced statement from which both physicians and surgeons may form a personal opinion on the indications for operation and the limitations of surgical treatment of hypertension. An extensive bibliography covers the Continental, American, and British references equally well. This book can be recommended to all interested in this subject.

Practical Pharmacology

J. H. BURN, F.R.S., professor of pharmacology, University of Oxford. Oxford: Blackwell Scientific Publications. 1952. Pp. 72. 12*s*. 6*d*.

LABORATORY techniques in physiology and in pharmacology tend to vary widely from one centre to another. There are no standard equipment and methods for experiments. In chemistry and biochemistry, on the other hand, apparatus is stereotyped and readily available, and methods are standard and universally applicable. There are thus numerous textbooks on practical chemistry and biochemistry, but very few on practical physiology and pharmacology. This book is thus a valuable addition to a small band, and all the more welcome since it comes from the Oxford school of pharmacology. It should be realised, however, that, although the experiments described are relatively simple—they are intended for undergraduates fresh from a course in practical physiology—considerable previous knowledge, both theoretical and practical, is assumed. Even at that, although the experiments are carefully described, students will need the help of trained demonstrators throughout the course in order to obtain the maximum benefit from the book. To the physiologist it is gratifying to see how pharmacology is based on, and grows out of, a knowledge of physiology. The empirical is slowly but surely giving way to the rational. All teachers of practical pharmacology will be glad to have this book and will look forward to a somewhat extended text in the future, with, let us hope, an index.

Der muskuläre Schiefhals beim Neugeborenen

Dr. HELMUT KASTENDIECK. Leipzig: Thieme. 1952. Pp. 72. D.M. 7.

THIS monograph on torticollis is the result of observations over the past forty years. Dr. Kastendieck claims that the cause is usually what in Great Britain we call a moulding deformity. He is able to point to associated asymmetries of the head and face and he backs up his theories with observations from the obstetric angle.

Leonardo da Vinci on Movement of the Heart and *Blood*

K. D. KEELE, M.D., F.R.C.P. London: Harvey & Blythe. 1952. Pp. 142. £4 4*s*.

THE tragedy of Leonardo da Vinci's life is that so much of the writings of this remarkable man, perhaps the greatest intellect of which we have any historical record, has been lost. That which remains is often fragmentary and so ill-arranged that its meaning is often obscure. For twenty years Dr. Keele has been engaged in historical research on the records left by Leonardo; and the fruits of his work in one branch of knowledge—the anatomy and physiology of the heart and blood-vessels—are embodied in this beautiful monograph. Dr. Keele has arranged the notes in a logical sequence and interpreted them, showing their bearing on subsequent discoveries in this department of medicine. Leonardo's own discoveries, and his insight into function, are almost incredible for the age in which he lived and the beliefs then prevalent.

He established the fact that the wall of the heart is made up of muscle, though he did not describe accurately the arrangement of the fibres; he described four chambers in place of the generally accepted two; he disproved the idea that air entered the heart; he described accurately the trabeculæ carneæ, papillary muscles and moderator band, and the coronary vessels. He made a model of the aortic valves, and through the glass aorta watched the action of the cusps under the current of blood. His illustrations of the heart in systole and diastole have never been surpassed. But he persisted in the error that there was a porous connection between the two ventricles. His drawings of the blood-vessels were well in advance of his time, and he described the changes of arteriosclerosis.

Dr. Keele's assessment of Leonardo's whole activity in art and science is startling. He describes it as "the epitome of greatness in failure," bringing forward in support of this view the flaking of the wall bearing *The Last Supper*, the destruction of the equestrian statue of Francesco Sforza by war, the over-painting of the Battle of Anghiari by Vasari, the unfinished state of the Mona Lisa, and in science, the failure of attempts at flight. Keele says there is no more doubt about the greatness of Leonardo's work on the heart and blood-vessels than about its essential failure. But Leonardo not only foresaw in the future such achievements as flying and submarine travel—he actually worked out practicable methods which became possible as soon as the petrol engine was invented: the principles of flight were all there. This can scarcely be called failure. His contributions to the function and structure of the heart were new, and have withstood the test of time. It is true he did not destroy all the errors prevalent in his time; but how can this be regarded as failure? His researches undoubtedly contributed to the discovery of the circulation of the blood by Harvey. The truth is that Leonardo was five hundred years before his time. That his equestrian statue was destroyed, many of his manuscripts lost, his painting obliterated by Vasari, have nothing to do with his essential merit. Leonardo forecast and prepared the way for the work of such giants as Galileo, Newton, and others; and when we consider how, in addition, he excelled in painting, sculpture, engineering, and biological science we begin to see how greatly he towered above even these other great geniuses. But though we may not agree with Dr. Keele's dispirited view of the facts, we can be thrilled by the way he presents them in this delightful book.

Surgical Practice of the Lahey Clinic

FRANK H. LAHEY, M.D., and members of the Staff of the Lahey Clinic, Boston. Philadelphia and London: W. B. Saunders. 1951. Pp. 1014. 75*s*.

THIS handsome volume shows to what a remarkable degree of success standardisation of operative methods can lead, for the results reported bear comparison with the best surgery anywhere in the world. A patient who enters the Lahey Clinic knows at least that he will get treatment of a high level of efficiency. Yet it is true that originality is always individual—a departure from pattern—and progress must always to some extent be denied to surgeons constrained to operate in a prescribed fashion, though they may extract to the limit the possibilities of one particular technical procedure. Evidently at this clinic advantage is taken of any advances originating anywhere else, and new procedures are quickly evaluated, as these excellent reports show.

This book is of absorbing interest. Everything is discussed with great frankness—including such difficult parts of surgery as the repair of the bile-ducts, where the results of no less than 229 repairs are reported. Experiences with modern vascular, thoracic, and neurological surgery are recorded, and the routine surgery of hernia, on which the last word has not been said, is not neglected. Indeed valuable information about every department of surgery can be gleaned from these pages, and the book is not one that will collect dust.

Indian Hemp

A Social Menace. DONALD McI. JOHNSON, M.A., M.B., B.CH., barrister-at-law. London: Christopher Johnson. 1952. Pp. 112. 8*s*. 6*d*.

INDIAN hemp, hashish, or marihuana, to give cannabis indica some of its more popular names, has attracted public attention lately and has been the subject of sensational press reports both in the U.S.A. and in this country in view of its threat to become a drug of addiction among young people.[1]

In New York the smoking of marihuana cigarettes ("reefers") by "teen-agers," encouraged in its use by dope pedlars as a preliminary to introducing them to heroin, has caused widespread concern and has resulted in the tightening of anti-narcotics legislation. In France, the Académie Nationale de Médecine has recommended that cannabis indica should no longer be imported, as it has hardly any place in modern therapeutics.[2] Undesirable as the drug may be, its addicts are apparently drawn only from socially and economically depressed classes who find in it some measure of escape from drab reality or use it to enhance the normal fantasy-weaving of adolescence. In the New York reports, most of the addicts were young Negroes or Puerto Ricans, and it is doubtful whether the drug would have much appeal to a normal well-adjusted person.

Dr. Johnson has reviewed the literature fully, and he provides quotations both from scientific publications and more literary accounts such as those of Théophile Gautier and Baudelaire. He has also assembled a body of data on the clinical effects of the drug which should be of general interest. Unfortunately, he is not content to present facts but embarks on a series of imaginative flights. He devotes one chapter to an apparently serious consideration of hashish as the drug for the "perfect crime," the victim being driven mad by small undetectable doses of it and confined sine die in a mental hospital by psychiatrists who are presumably incapable of differentiating between toxic delirium and psychosis. He also speculates whether the change in the Russian temperament is not due to widespread admixture of the weed with the Soviet wheat, and is concerned at our importation of Russian wheat lest the poison should be introduced into our bellies and brains.

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1. *Lancet*, March 29, 1952, p. 654.
2. *Bull. Acad. Méd. Paris*, 1952, 136, 134.

THE LANCET

LONDON: SATURDAY, MAY 31, 1952

The Queen

THREE months ago the thoughts of all of us turned to our new Queen. Her father's life and death had made us conscious of the continuing and growing importance of the Monarchy as the centre of our nation and of our family of nations; and we recognised the magnitude of the task falling to his successor. Today, as the period of mourning ends and THE QUEEN enters more fully into the public life of her people, there is everywhere a strong desire that too much should not be asked of her. As mother of a young family and mistress of a home, she has a life of her own whose happy fulfilment her subjects would place first. Already thus occupied as parent and wife, she now becomes permanent head of the Governments of her several realms, and must gradually acquire the knowledge and experience of their affairs which is needed even by the most constitutional of monarchs, together with the range of interests appropriate to the most representative of citizens. Finally, as Sovereign, she must discharge the ceremonial functions of Royalty; and it is here, especially, that precautions are required. The grace and gaiety shown by the PRINCESS ELIZABETH on her travels has made many forget how great can be the strain of ceremonial engagements, particularly when in series. For anyone who performs them as well as THE QUEEN, her functions must have their enjoyable side; and all have observed with pleasure her natural aptitude for her vocation. Her personality indeed is such that every public appearance must strengthen the bonds between Throne and People. But, during the next few years at least, her advisers would do well to resist all calls for her official presence except on really great occasions. Of late the medical profession has become more and more aware of the physical price paid by those subjected to too frequent or continuous strain of the kind nowadays imposed on Royalty. As doctors, therefore, we should have special reason to welcome an assurance that, by deliberate decisions taken in advance, HER MAJESTY's health and vitality will be protected from HER MAJESTY's hereditary sense of duty.

New Approaches to Hepatic Cirrhosis

THE treatment of cirrhosis of the liver and its complications has been getting a great deal of attention both here and in the U.S.A., where alcoholic cirrhosis is much commoner than in England. BLAKEMORE and colleagues [1] advocate a direct anastomosis between the portal vein and the inferior vena cava, to divert the portal blood into the systemic circulation and so lower the pressure in the portal system, which is nearly always high in cirrhosis. In this way it is possible to relieve ascites and lessen the risk of hæmorrhage from œsophageal varices. Technically, however, venous anastomoses of this type are often very difficult, which is not altogether a bad thing if it means that only experts undertake them. Not everyone has had results comparable with those of BLAKEMORE, whose team has had the largest experience in this field; and the practical difficulties, together with doubts about the long-term value of the operations, have led others to look into the basic causes of portal hypertension in the hope of devising simpler treatments.

The normal pressure in the portal vein, taken during laparotomies for non-hepatic conditions, is 85–150 mm. of water or 6–12 mm. Hg, though, as Prof. MILNES WALKER remarked when reporting these findings in his lecture published in our issue of April 12, the pressure in healthy people almost certainly varies considerably with changes in the blood-flow through the abdominal viscera, and opening the abdomen may also affect it. Portal hypertension may arise from prehepatic or intrahepatic obstruction of the portal vein or its tributaries, or from posthepatic obstruction of the hepatic vein, such as occurs in right-sided heart-failure. A definite localisable block in the portal venous system is rarely found; thus at last year's Ciba symposium, MACPHERSON [2] discussed 128 cases of portal hypertension seen at BLAKEMORE's clinic or with LEARMONTH in Edinburgh and his list showed a defined venous block in only 17. Most cases were attributed, somewhat vaguely, to intrahepatic block. Searching for causes of this condition, BERMAN and colleagues in Indianapolis [3] have turned back to the early work on the distortion of the circulatory system inside the liver accompanying the cirrhotic process. In the normal liver the central veins of the lobule receive blood from both the hepatic artery and the portal vein, and the terminal vessels of the two systems alternate in an orderly manner; except at the actual emptying points into the central veins, an exchange between the two systems only occurs across the sinusoidal beds. By injection techniques MCINDOE [4] showed that in cirrhosis the vessels of both portal and hepatic systems are distorted and the terminal vessels lose their orderly alternation and become entangled in a basket-like mesh of fine channels. Collateral vessels arising from the portal vein before its terminal stages divert portal blood away from the liver. His perfusion experiments demonstrated that with a portal pressure of 20 mm. Hg (27 cm. water) 87% or more of the perfusion fluid passes directly into the collateral vessels and is thus shunted directly into the caval system; the most that passes through the liver to the hepatic veins is 13%. Epplen[5] showed that in cirrhosis intrahepatic communications form between the hepatic artery and the portal venous system. These are important because normally the relatively high pressure in the hepatic artery restricts the flow through the low-pressure portal system, and this effect can be exaggerated in cirrhosis. Dock[6] perfused the portal vein with kerosene at a pressure of 20 mm. Hg (27 cm. water) and studied the effect of occluding the hepatic artery and then opening it at a pressure of 100 mm. Hg. In a normal liver, opening the hepatic artery reduced the flow through the portal vein by 30%; in a case of alcoholic cirrhosis the reduction was 78%, but in "non-alcoholic cirrhosis" the fall was within normal limits (28%). From these experiments it seems clear that the pressure in the portal vein must be over 27 cm. of water to maintain the portal flow in alcoholic cirrhosis.

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[1] See leading article, *Lancet*, 1951, ii, 871.

[2] Macpherson, A. I. S. Ciba Foundation Symposium on Liver Disease. London, 1951; p. 145.

[3] Berman, J. K., Koenig, H., Muller, L. P. *Arch. Surg.* 1951, 63, 377.

[4] McIndoe, A. H. *Arch. Path.* 1928, 5, 23.

The experimental findings suggest, in the view of Berman et al.,[3] that cirrhosis of the liver has somewhat the same effect as an arteriovenous varix, in which a high arterial pressure is communicated directly to the veins and slows their outflow of blood. In the liver the effect is to cause portal hypertension and hence to deflect blood into the familiar collateral vessels leading to the caval system—œsophageal, rectal, and retroperitoneal, sometimes distending the peri-umbilical veins en route to form a "caput medusæ." Moreover, this deflection of blood from the liver, perhaps aided by abnormal communications between hepatic artery and veins, may seriously deplete the liver itself of nourishment and so help to perpetuate and accelerate the cirrhosis. It follows, according to Berman et al., that portal hypertension should be treated like other arteriovenous varices—by occluding the supplying artery; in this case the hepatic artery. Unfortunately tying the hepatic artery has usually led to necrosis of the liver. Chau et al.[7] have lately shown, however, that in dogs the necrosis results from a widespread clostridial infection and can be largely prevented by previous administration of antibiotics. Berman et al. have confirmed the protection given by antibiotics in dogs and have found that the necrosis depends on the site of the ligature—if the artery was tied close to the liver necrosis invariably followed, but the dogs protected with antibiotics survived ligation of the artery at its source, though the resultant fall in their portal pressure was only 1–2 cm. of water. Since 25–40% of the portal blood comes from the spleen, Berman et al. next ligated both the splenic and hepatic arteries, which produced a sustained fall in portal pressure.

Ligation of the hepatic and splenic arteries near their origin from the cœliac axis seems the most successful of the experimental procedures, and Berman and colleagues thought it justifiable to try it in man. They have done the operation on 10 patients with advanced cirrhosis producing ascites and œsophageal varices, with good short-term results. In a later paper they describe one case in detail.[8] A man of 60, with severe alcoholic cirrhosis and ascites that needed frequent tapping in spite of adequate medical treatment, was given 600,000 units of penicillin and 1 g. of streptomycin daily for two days before and ten days after the operation. He recovered very well, and a slight recurrence of his ascites seven weeks after the operation was easily controlled by restricting his salt intake to 3 g. daily. The same treatment has been tried by Rienhoff[9] at Johns Hopkins who reported results in 6 patients. The first operation was done in 1947 for gross alcoholic cirrhosis and severe ascites; at the time of the report 3½ years later there had been no further ascites despite the patient's return to his whisky. Then a sherry drinker of 59, operated on after a severe hæmatemesis, seemed well a year later; he had had no more bleeding, and an abdominal arteriogram showed no filling of the liver, so the hepatic artery was still occluded. A third patient, who had had nine exsanguinating hæmatemeses before the operation, kept well for seven months afterwards. In a somewhat similar group reported from France by Leger et al.[10] only the hepatic artery was ligated; there has been one postoperative death; but a woman of 42, operated on for ascites and œdema, recovered so well that, six months later, "elle supporte bien la viande grillée midi et soir. . . ." Leger notes that about 20 ligations have now been reported.

Any competent abdominal surgeon could tie the hepatic and splenic arteries, though he would not tackle a portacaval anastomosis. But surgeons who think of trying the ligation operation, and physicians who might recommend it for their patients, should first study the published facts. Up to now the operation has been done only for gross cirrhosis, mostly directly attributable to alcoholism, which has reached the stage of ascites, sometimes with bleeding œsophageal varices also. Few patients have been followed for longer than a year, and none for more than 3½ years. These patients have nothing to lose; and, even if they develop liver failure later, they will have been made comfortable for a fairly long time. It is justifiable to operate on them; but patients with "splenic anæmia" are a different matter. This condition affects young adults and children; bleeding from the œsophagus is its main symptom, and liver biopsy often shows only slight cirrhosis. Splenectomy, which is the usual method of treatment, probably acts by reducing the portal blood-flow. Portacaval anastomosis is sometimes performed, solely with the aim of lessening the risk of serious hæmorrhage; but it is still too soon to say whether the results will be any better than after splenectomy. Until we know more about the long-term effects of ligating the hepatic and splenic arteries, this operation should be restricted to the severest cases of cirrhosis.

For relieving the symptoms of hepatic cirrhosis, arterial ligation has a firmer theoretical basis than portacaval anastomosis, besides being much easier to perform. If the results claimed by Berman and other surgeons are confirmed, ligation will probably oust portacaval anastomosis altogether. One can only condole with those who have worked hard to perfect this operation, and now may see it replaced by a far simpler newcomer.

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5. Epplen, F. *Arch. intern. Med.* 1922, 29, 482.
6. Dock, W. *Trans. Ass. Amer. Phys.* 1942, 57, 302.
7. Chau, A. Y. S., Goldbloom, V. C., Gurd, F. N. *Arch. Surg.* 1951, 63, 390.
8. Berman, J. K., Muller, L. P., Fisch, C., Martz, W. *Ibid*, p. 623.
9. Rienhoff, W. F. Jun. *Bull. Johns Hopk. Hosp.* 1951, 88, 368.
10. Leger, L., Albot, G., Oudot, J., Zerolo, J. *Pr. méd.* 1952, 60, 176.

Leads in Electrocardiography

THE introduction of V leads and precordial leads[1–3] has greatly modified the theory and practice of electrocardiography. The standard leads, though they gave surprisingly accurate results, had two disadvantages: they were bipolar, measuring differences of potential between two limbs; and they were remote from the heart and unable to give more than a general picture of its electrical activity. Moreover the deflections could not be accurately analysed, because the nature of their components was unknown. This was no great difficulty with the simple auricular waves, but it was of importance with the complicated QRST pattern of the ventricles. In lead I, for example, an upright deflection merely indicated that the left arm was more positive than the right; it might theoretically be caused either by a large positive deflection in that arm or by a large negative deflection in the right arm, or by varying combinations of both. Similarly a downward deflection, such as a Q wave in lead III, might depend upon either a negative left foot or a positive left arm. In practice the almost constantly negative potential of the right arm reduced some of the possible difficulties, but they still prevented any real understanding of the electrocardiogram.

In 1934 Wilson et al.,[1] accepting Einthoven's assumption that the sum of the electrical potentials of the three other limbs was zero, connected each of them through a resistance to a central terminal which they regarded as at zero potential. By pairing this terminal with electrodes on the limbs they obtained unipolar leads, which were called voltage or V leads, because they recorded the actual potentials of the right arm, the left foot, and the left arm (V.R., V.F., V.L.). This unipolar technique was simplified by Goldberger,[4] who paired the exploring electrode with another connected only to the two remaining limbs. He showed that his results were nearly equivalent to Wilson's overstandardised by half. As the deflections of Wilson's lead were inconveniently small, Goldberger's method was widely adopted. The validity of Wilson's claim has been criticised,[5] but there is enough evidence to show that the V leads are nearly unipolar and that the effect of the neutral electrode is virtually negligible. A precordial lead, wherever the distant electrode may be, is also practically unipolar, and records, almost exclusively, the electrical activity of the myocardium immediately beneath it. These leads have established the basic electrical patterns of the epicardial surfaces of the two ventricles[6]—namely, an rS, sometimes with an inverted T, over the right ventricle, and a qR with an upright T over the left. The right-ventricular pattern is generally found in positions 1 and 2 of the conventional exploring sites, and the left-ventricular pattern in positions 5 and 6, while positions 3 and 4 may show intermediate or transitional complexes. The unipolar limb leads usually resemble the chest leads; leads from the left arm and left foot give pictures like those of the left chest leads, and those from the right arm correspond to right chest leads or to the QS-inverted-T pattern obtained from the cavity of the ventricle. Both they and the precordial leads vary considerably with the electrical position of the heart. Anatomically, the heart is free to move in several ways, the most important being rotation about its anteroposterior axis and about its long axis. Its electrical and its anatomical positions are closely, but not exactly, related. Rotation about the anteroposterior axis, producing a horizontal or a vertical heart, affects chiefly the limb leads. Conversely, rotation about the long axis affects mainly the precordial leads. In practice the two movements are generally combined. By correlating these patterns with the known direction of spread of the cardiac impulse, it has been possible to show that the heart, making due allowance for its complex structure, behaves electrically in the same way as a single strip of contracting muscle.

The principles derived from unipolar electrocardiograms have clarified much that was formerly obscure in the standard leads, and have demonstrated the important effect of position on the electrocardiogram. Axis deviation, which was thought to mean hypertrophy or enlargement of one or other ventricle, is now regarded primarily as a sign of rotation of the heart about its anteroposterior axis, with or without pathological change. A horizontal heart, because of the tall R wave in the left arm lead and the deep S wave in the foot lead, produces the characteristic electrocardiogram of left axis deviation, while the reverse pattern of right axis deviation is given by a vertical position. A deep Q wave in lead III, simulating posterior infarction, is another abnormality that may be found with a horizontal heart, while a low or flat T wave in lead I, suggesting high lateral infarction, may be caused by a vertical heart. In such cases the unipolar leads should theoretically be helpful because they can determine the position of the heart. In practice they are seldom necessary, for such information can almost equally well be obtained from the standard leads. Axis deviation adequately fixes the position of the heart, the changes in lead III due to posterior infarction can nearly always be confirmed in lead II, and a T wave that is lower in lead I than in lead III should only suggest a lateral infarct if there is no right axis deviation. The unipolar limb leads will seldom do better. Precordial leads on the other hand are firmly established. There is little to choose between V leads and chest leads paired with the right arm (C.R.), but chest leads paired with the foot (C.F.) vary considerably owing to the unpredictable potentials of the left foot, and inversion of the T wave in health may limit their usefulness.[7] It is logical to prefer V leads. The greatest usefulness of chest leads is in ventricular abnormalities. Not only can they detect localised disease of the anterior and lateral surfaces of the heart, but also they can amplify the information given by the standard leads. They can distinguish axis deviation from ventricular hypertrophy, particularly of the left ventricle, and they are valuable in the diagnosis of intraventricular conduction defects, especially right bundle-branch block. In the localisation of infarction other than the posterior type, and its differentiation from other causes of T wave inversion, they are indispensable. Without their assistance anteroseptal, posterolateral, and high lateral infarcts may be missed, because their effects

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1. Wilson, F. N., Johnston, F. D., Macleod, A. G., Barker, P. S. *Amer. Heart J.* 1934, 9, 447.
2. Wolferth, C. C., Wood, F. C. *Amer. J. med. Sci.* 1932, 183, 30.
3. Wilson, F. N., et al. *Amer. Heart J.* 1944, 27, 19.
4. Goldberger, E. *Ibid*, 1942, 23, 483.
5. Wolferth, C. C., Livezey, M. M. *Ibid*, 1944, 27, 764.
6. Wilson, F. N., Macleod, A. G., Barker, P. S. *Ibid*, 1932, 7, 305.
7. Leatham, A. *Brit. Heart J.* 1950, 12, 213.

on the limb leads are variable. Chest leads provided the only evidence of abnormality in 40 out of 300 electrocardiograms of patients with infarction.[8] Multiple leads should always be preferred to a single apical lead. When there is a possibility of right ventricular hypertrophy or of anteroseptal infarction positions 1, 3, and 5 are advisable, but otherwise positions 2, 4, and 6 explore a more useful part of the heart.

The standard electrocardiogram has been challenged by the newer methods, but it has not been superseded for routine use. The unipolar limb leads are only occasionally necessary, and it has been said that they have served us best by contributing to our understanding of the standard leads.[9] Multiple chest leads have added greatly to the value of electrocardiography whenever there are signs of heart-disease, and they are almost imperative when coronary disease is suspected. On the other hand, serious heart-disease, rheumatic or hypertensive, can exist with a normal electrocardiogram, and even healed infarction can go undetected, especially when there are signs of left-ventricular hypertrophy.[10] Electrocardiography is undoubtedly more informative than it was, but it is still only one link in the diagnostic chain.

William Stewart Halsted

THAT we in this island should wish to pay tribute to W. S. HALSTED, the great American surgeon, in the year which marks the centenary of his birth, is natural. His family came from here, and the loss which we suffered in the year 1660 from the export of such vigorous stock has in part been repaid by the great and abiding influence which its descendant has had on surgical methods everywhere. Halsted centenary celebrations are naturally an American affair first and foremost, and the major ceremony took place earlier this year at the Johns Hopkins Medical School, where the Royal College of Surgeons and the Royal Society of Medicine were jointly represented by Mr. D. H. PATEY. Last week Mr. PATEY, as president of the surgical section, presided over the Halsted centenary meeting of the Royal Society of Medicine. The occasion was impressive. The president of the society, Lord WEBB-JOHNSON, wearing the robes in which he is portrayed in this year's Academy at Burlington House, welcomed America's delegates in the persons of Dr. ALFRED BLALOCK, present holder of Halsted's chair at Johns Hopkins, and Dr. S. J. CROWE, the distinguished otolaryngologist and a personal friend of Halsted.

Dr. BLALOCK told of Halsted's early life, of his years as a surgeon in New York, and of his translation to Baltimore to become professor of surgery. He spoke of Halsted's contributions to surgery in his studies of wound infection and healing, of vascular surgery, of intestinal anastomosis, of local anæsthesia, and of the surgery of inguinal hernia, goitre, and carcinoma of the breast. He ended by presenting to Sir CECIL WAKELEY, for the Royal College of Surgeons, a copy in oils of the well-known Halsted portrait. Dr. W. R. BETT next described the paradox of Halsted's life with his transition from a busy New York surgeon, vigorous, quick, didactic, and rather showy, to the meticulous, fastidious, and refined person, who operated carefully and exactly, in the academic atmosphere of the new department of surgery at Baltimore. He ascribed this change to the stern but successful battle which Halsted waged with himself to break his cocaine addiction—a habit he had acquired in his pioneer and often personal experiments on regional nerve-block anæsthesia with cocaine before he realised its dangers as a drug of addiction. Dr. S. J. CROWE gave the meeting some delightful personal stories of Halsted and deftly illuminated his character and private life. At the conclusion of his address, Dr. CROWE presented a walking-stick of Halsted's to Lord WEBB-JOHNSON for the Royal Society of Medicine. Mr. R. S. HANDLEY, reading the last paper of the evening, gave the results of his investigations of the internal mammary lymph-chain in carcinoma of the breast—a subject of which Halsted spoke in one of his papers but did not pursue. Mr. HANDLEY had found that of 119 cases of carcinoma of the breast 34% showed invasion of the chain. He remarked, however, that the chief purpose of the evening was not to discuss technical points but, in the words of the Apocrypha, to "praise famous men and our fathers that begat us."

Halsted's contributions on individual surgical problems were so many and important as to place him in the front rank among the surgeons of the world. But probably greater than these was his influence on the technique of surgery and the attitude of surgeons towards their art—the precise diagnosis, the careful preparation before operating, and the unhurried operative technique, with concentration on hæmostasis and the gentle handling of tissues which is so inimical to the ambitions of those who seek to break speed records in the operating-theatre. He taught by example that operations were for the good of the patient, not the glory of the surgeon, at a time when the reverse view was the more fashionable. By his pupils he secured the propagation of his methods throughout America and the world. He used to say that he found the greatest satisfacton of his life in training surgeons; and the group of men he trained must, in their numbers and in the brilliance of their later achievements, be without equal. This is his greatest monument.

Aureomycin

ADMINISTRATION of aureomycin by mouth commonly causes anorexia, nausea, and vomiting. These symptoms can be alleviated by giving antacids or buffering agents such as milk, calcium carbonate, sodium bicarbonate, or a mixture of mucin, aluminium hydroxide, and magnesium trisilicate. Some of these, such as sodium bicarbonate and milk, are not suitable for patients needing a diet restricted in sodium. Moreover, the simultaneous administration of aureomycin with other preparations is troublesome and may be confusing, so that much can be said for incorporating the antibiotic and antacid in the same preparation. This has been done by Manning and Wellman[1] of the Mayo Clinic, with tablets containing aureomycin calcium caseinate 125 mg., calcium caseinate 200 mg., and calcium carbonate 50 mg. Serum-aureomycin levels were comparable with those after the same dose of aureomycin alone, and the incidence of nausea and vomiting was considerably decreased; of 24 patients only 3 experienced these side-effects.

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[8] Roche, E. H. *Ibid*, 1945, 7, 119.
[9] Katz, L. N. *Circulation*, 1950, 2, 94.
[10] Levine, H. D., Phillips, E. *New Engl. J. Med.* 245, 833.

[1] Manning, P. R., Wellman, W. E. *Proc. Mayo Clin.* 1952, 27, 89.

Annotations

W.H.O. IN 1951

THAT the World Health Organisation is now a sturdy child is demonstrated by the need for 200 double-column pages in the directors' report for 1951.[1] Dr. Brock Chisholm, the director-general, records a further development of "world health consciousness." There is a widespread opinion that it is "the duty of those countries more richly endowed with resources and more skilled in their use and conservation to help those less developed to provide the scientific and medical means of improving the health of their peoples." This is no longer an ideal limited to a hopelessly small number of missionaries and humanitarians; it has the practical support of 69 countries who subscribed nearly six million dollars to the funds of W.H.O. last year. The United Kingdom's share was the sterling equivalent of $815,452.

Basic work on epidemiology, environmental sanitation (which "remains the bedrock of the preservation of health)," and drugs and therapeutic substances is being continued. The scope of W.H.O.'s work is now so large that detailed direction from Geneva is no longer practicable. Six regional headquarters have been set up—in Africa, the Americas, South-East Asia, Europe, the Eastern Mediterranean, and the Western Pacific. Autonomy and opportunity for initiative exist within these regions, and this administrative decentralisation will undoubtedly contribute to a more stable and efficient organisation.

Of the many plans being put into action, two involve new methods of special interest. There is the bold attempt to eradicate yaws from heavily infected populations by examining every person and systematically treating those infected. This work has started in South-East Asia, and in the first half of 1951 alone over half a million people were examined in Thailand and Indonesia by local teams under international guidance, and 140,000 cases of yaws were discovered and treated with penicillin. The aim is that every inhabitant of these countries should be examined. This immense task is in the hands of a team; the expert consultative staff is supplied by W.H.O., the local staff by the national governments, and most of the penicillin, the necessary jeeps (the camels of the jungle), and the administrative help by UNICEF. There is also the first serious attempt to deal with the problem of excessive population on an international scale. The W.H.O. regional committee for South-East Asia, with the help of the government of India, has set up a pilot experiment in the use of "the rhythm method" of population control. Such an experiment is fraught with difficulties, both educational and physiological. Both W.H.O. and the government of India have shown courage and vision in undertaking an experiment which must be regarded by many experienced critics as attempting the impossible. The venture is well worth while, even if the pilot experiment has only a limited success, for it will point the way to other means of studying the growth and control of large populations—a problem fundamental to world health—and it should advance our knowledge of maternal and child health.

W.H.O. also teaches by collecting, sorting, and distributing technical knowledge. Seventeen international training courses were organised last year; these included one in London on the reablement of physically handicapped children, another in Calcutta on nutrition, and a medical teaching mission to Iran. During the year 655 fellowships were granted to nationals of 73 countries.

The report is a record of solid achievement. The one black spot is the list of "inactive members": China, the Soviet Union, and other eastern European countries. Despite this unfortunate gap, the United Nations has proved itself capable of promoting international coöperation for the good of the world's health. None but the unduly pessimistic can fail to be heartened by reading of these attacks by "international teams" on fundamental human problems.

EXPERIMENTAL PULMONARY HÆMOSIDEROSIS

THE interesting experimental work [1] done by Dr. F. R. Magarey in the department of pathology of the Welsh National School of Medicine justifies a postscript to our leading article of May 17. Lendrum and his colleagues [2] believe that the focal deposits of siderophores are the result of bleeding into the lungs from the mucosa of the terminal bronchioles at the site of the anastomoses between the bronchial and pulmonary circulations. Magarey has shown that blood injected endotracheally into the lungs of rats is at first widely distributed, but later it collects in groups of alveoli as aggregates of intracellular hæmosiderin like those seen in human pulmonary hæmosiderosis. Some animals received a single injection of blood, while others had repeated injections over a period of months. In those rats killed immediately after injection, the blood was distributed diffusely through large areas of the lungs. Some rats were killed two days after injection; many phagocytes were found in the alveoli, a lot of them containing red cells, but a few red cells were still free in the alveoli. At this stage large extracellular crystals of hæmoglobin were present. Four days after injection the phagocytes, which tended to congregate in clumps, contained a few minute hæmosiderin crystals. After a week the phagocytes were full of hæmosiderin, and the hæmoglobin crystals had disappeared. By ten days most of the siderophores had collected in small groups, and at fourteen days the aggregation was even more noticeable, but there were still a few phagocytes irregularly scattered through the lung.

In the rats which had had repeated injections for about thirteen weeks, small clusters of alveoli packed with pigment-bearing phagocytes were seen in the region of the alveolar ducts, while the neighbouring alveoli were almost free of cells. Some animals were killed immediately after the last injection, and in these the discrete aggregations of siderophores were surrounded by red cells diffusely distributed in many alveoli. But nine months after the last injection, focal collections of siderophores were fairly evenly scattered through the lungs; there were rather more in the dorsal parts, suggesting that gravity had little or no effect on their distribution. A few deposits of hæmosiderin were found in the perivascular and peribronchial interstitial tissue, but most of the pigment was in alveoli well away from these sites. Magarey points out that his experiments suggest that collections of hæmosiderin-containing phagocytes, such as those seen in the lungs in mitral stenosis, may be the result of diffuse hæmorrhage within the lungs. He rightly says that there are small differences in the minute anatomy of the lung in man and rat, but that the similarity of the appearances is close enough to conclude that the fundamental process is the same in both. His experiments, however, do not mean that Lendrum and his colleagues are necessarily wrong about the source of the bleeding in human hæmosiderosis. They were dealing with abnormal human lungs, and Magarey with those of healthy rats. Much remains unexplained; why, for instance, is there widespread diffuse distribution of hæmosiderin in some cases, and in others focal accumulations? This fact alone shows that red cells, widely scattered in the lungs, are not always collected into aggregates. Magarey's experiments,

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[1] The Work of W.H.O. Annual report of the director-general W.H.O. Geneva. 1952. Pp. 200. 9s. Obtainable from H.M. Stationery Office.

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[1] Magarey, F. R. *J. Path. Bact.* 1951, 63, 729.

[2] Lendrum, A. C., Scott, L. D. W., Park, S. D. S. *Quart. J. Med.* 1950, 19, 249.

like those of Strassmann[3] on the influence of pulmonary œdema on the removal of extravasated red cells from the lung, give a valuable stimulus to the elucidation of the pathological changes in man.

INDUCED CONVULSIONS PROLONGED BY OXYGEN

THE use of induced convulsions in psychiatry, whatever its therapeutic merits, was bound sooner or later to throw light on the problem of epilepsy in general. Some striking observations with induced convulsions in animals have lately been reported from Freiburg. In 1949, Richard Jung developed a method of registering, by the insertion of bipolar electrodes into various sites of the cat's brain, the electrical potentials during and after chemically or electrically induced convulsions.[4] He found an enormous increase of electrical activity in the brain during the fit, amounting to 20–50 times the normal. Hugo Ruf,[5] who was working with Jung, drew the reasonable conclusion that this betokened a great increase in cerebral metabolism whereby all available oxygen was used up. Moreover, the oxygen supply may be further impaired by the laryngospasm that commonly accompanied the fit as well as the brief interruption of breathing at the end of the fit. The electrical silence of the cortex at about the same time, Ruf also interprets as due to oxygen lack. If this is so, a continuous excessive supply of oxygen and an increase in the cerebral blood-supply should prolong the convulsion. Ruf carried out many experiments on cats, and he confirmed this hypothesis. An electrically induced convulsion usually lasted about 1 minute, but it was possible to prolong it to 3 minutes by insufflation of oxygen, and to as much as 13 minutes by tracheotomy and injections of 0·1 mg. of adrenaline every 3–4 minutes. The period of post-convulsive electrical silence was abolished in these experiments. In order to intensify the effect of adrenaline, Ruf gave the cats phenyl-methyl-aminopropan, an inhibitor of amino-oxydase, the enzyme which oxidises adrenaline. When the convulsion had almost died down and the animal appeared exhausted, it was possible to provoke a new, strong, and prolonged tonic-clonic discharge by insufflating oxygen alone. Similarly, an injection of adrenaline, though it never gave rise to a convulsion, renewed electrical activity in an animal which had previously had 3 mg. of phenyl-methyl-aminopropan. The prolonged convulsive activity in various parts of the brain—as long as 33 minutes in some areas—allowed many interesting and new observations to be made on the localisation of the electrical discharge. After general stimulation of the brain by electricity, as in electroconvulsive therapy, the focus of greatest electrical activity was found to shift from one hemisphere to the other every 1–3 minutes. If the convulsion was induced chemically—e.g., by leptazol—no wandering focus was detected: periods of maximum discharge alternated with periods of rest, and no one area of the cerebral cortex seemed particularly active, even when the leptazol convulsion was prolonged by the methods described. But in electrically induced fits the thalamus and the cornu ammonis showed the greatest convulsive tendency. The most persistent activity of all was found, quite unexpectedly, in the cerebellum; when oxygen was given continuously the cerebellum went on discharging for 30–50 minutes after all activity elsewhere in the nervous system had stopped.

The performance of the brain in artificially prolonged convulsions encouraged Ruf to try a practical application. He used oxygen insufflation and his method of circulatory stimulation to revive patients with cerebral œdema after injury or operation, when the usual methods had failed.

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[3] Strassmann, G. *Arch. Path.* 1944, 38, 76.
[4] Jung, R. *Arch. Psychiat. Nervenkr.* 1949, 183, 206.
[5] Ruf, H. *Nervenarzt*, 1950, 21, 109; *Arch. Psychiat. Nervenkr.* 1951, 187, 97; *Nervenarzt*, 1951, 22, 437.

SIMPLE TEST FOR BLOOD IN FÆCES

TRADITIONALLY the physician undertakes side-room tests; but in the last few years this has become less usual, especially in the former local-authority hospitals which are being upgraded. This transfer of the simpler tests to the main hospital laboratories offers some gain, in that the tests used there are usually more delicate and more specific; for example, the tests for blood in urine commonly used on the wards are only a little more sensitive than inspection with the naked eye.[1] On the other hand, the laboratory worker may decide on a test so delicate that the patient has to be specially prepared, whereas the test favoured by the physician needs no preparation.

In tests for occult blood in fæces great sensitivity offers no advantage. The benzidine test in its usual form will prove positive if the patient has eaten meat during the previous day or two, so that he has first to go on a special diet for three days. What usually happens thereafter is that the specimen is collected by a nurse, placed in a container, and labelled, and is then taken by a messenger to the laboratory. There the patient's name is recorded by a clerk, and the stool is handed to a technician, who takes a sample, which is diluted with water, heated, and after cooling added to a benzidine-peroxide solution. After this malodorous and unhygienic process the report is written and sent through the hands of the clerk, messenger, and nurse to the physician, while some record must perforce be made in the laboratory and the container cleaned or destroyed. Not uncommonly the report is lost, so that hurried telephone calls and searches in the laboratory records become necessary. Such a procedure may be necessary for a few patients, but for the majority it is needlessly complicated.

Needham and Simpson[2] have shown how to eliminate some of this wastefulness. They have modified Gregersen's slide-test into one which requires for each patient about 30 seconds' attention by the physician in the outpatient clinic or 2 minutes' attention in his consulting-room. The test is not affected by diet unless the patient has recently eaten black pudding or fried liver; and if it is positive, it indicates bleeding into the gastro-intestinal tract in 11 cases out of 12. No special containers are needed, and the test is done on filter-paper, which can be burnt after use. Such a test is economical of labour, time, space, materials, and temper—and thus also of money.

Let us hope that comparable simplifications of other tests will become popular. Van Slyke's urea-clearance test is elegant, but usually it is a luxury; and both this and MacLean's urea-concentration test might be replaced for routine work by some form of concentration-excretion test, using specific-gravity determinations which require far less labour than does chemical estimation of urea. Furthermore, specific-gravity beads will determine the specific gravity of urine more quickly, accurately, and hygienically than will a urinometer. Thus routine assessment of renal function can for the most part be made in the ward side-room with a measuring cylinder and a set of specific-gravity beads.* Again, blood-sugar curves are rarely necessary for the diagnosis of diabetes mellitus; a single estimation of blood-sugar on a sample taken 2 hours after the end of the midday meal will usually settle the diagnosis.

Unfortunately registrars and housemen may not be easily persuaded to do side-room tests because the glamour of the "precise" laboratory test convinces many that even the simplest laboratory problem requires esoteric learning and cumbrous procedure. Personal experience in a laboratory would go far to dispel this misapprehension.

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[1] [illegible] *Brit. med. J.* 1951, ii, 774.
[2] [illegible] R. G. *Quart. J. Med.* 1952, 21, 123.
* [illegible] O. Blake Ltd., 40, Hatton Garden, London, E.C.1.

Clinical laboratories always need residents to deal with the emergencies at night, and there is no reason why housemen should not be selected for this work from those who intend to engage in clinical practice. Everyone would benefit from such a reversion to the ancient custom of the teaching hospitals.

POLIOMYELITIS IN ADULTS AND CHILDREN

THE broad epidemiological patterns of poliomyelitis have been changing. There has been a gradually increasing incidence of attacks, mostly paralytic, among adults, and a greater incidence (or perhaps wider recognition) of non-paralytic syndromes in children, although without serological tests illness due to other neurotropic viruses—notably that of mumps[1]—may be included under this heading.

These features are evident in two "hospital inquiries" made by the Ministry of Health in 1947 and 1949, and analysed by Bradley and Gale.[2] In the second inquiry it was found that of 7832 poliomyelitis admissions to hospitals in England and Wales the notified diagnosis was not confirmed in a third. Of the confirmed attacks 79% were paralytic, and nearly a third of these were in patients over 15 years of age; but two-thirds of the non-paralytic syndromes affected children under that age. During the epidemic season of the same year (1949) Weinstein and his associates[3] made detailed studies of the clinical features of the disease in 428 patients admitted to the Haynes Memorial Hospital, Boston, Mass., who were followed up for 3–18 months. In this series boys were more commonly attacked than girls, whereas among adults (patients aged 16 years upwards) women preponderated slightly "even when the increased susceptibility of the pregnant (estimated to be at least four times higher than expectancy) was considered." No mention is made of tonsillectomy and parenteral injections, which are held to predispose to bulbar palsies and elective paralyses of the extremities, respectively. Although most of the recognised clinical features were found at all ages, some showed significant quantitative differences in children and adults. Prodromata were most often lacking among the oldest patients; but whereas upper respiratory syndromes were commonest in the youngest children, gastro-intestinal and generalised "influenzal" symptoms were much more usual in adults. During the stage of invasion, stiffness of the neck was noted twice as often in patients over the age of 6 as in younger children; among these, on the other hand, diarrhœa was twice as common. Dysuria was recorded 4–13 times, paralysis of the bladder up to 10 times, and serious gastro-intestinal dysfunction (e.g., meteorism) 5–8 times more often in adults than in children. Rashes, of unspecified type, were observed approximately 19 times as often among the oldest patients as among those up to 15 years of age. Generalised lymphadenopathy (20% among the under-5s) decreased with age. Non-paralytic attacks (28% of the whole series) occurred most often in children. Spinal paralysis was commonest up to 5 years of age and least common among older children. Bulbar paralysis was observed about as often in children as in adults, but the bulbospinal type was somewhat commoner in adults.

When spinal and bulbar paralyses were grouped together the difference in frequency between children (66%) and adults (77%) was insignificant, but the type and degree of muscle dysfunction resulting from spinal paralysis and the levels affected by bulbar involvement varied widely with age. Thus, paralysis of one leg occurred predominantly in the 0–5 age-group, whereas paresis of one arm was most common among those aged 6–15. Quadriplegia did not occur among the youngest patients, and was 2·5–3 times more common among adults than older children. The dangerous diaphragmatic and intercostal forms were found most often in those aged 16–30 years. Bulbar paralysis (21·3% *in the* whole series) affected only 8% of the youngest children, compared with 31·6%, 27·7%, and 26·8% in the 6–15, 16–30, and 31–50 age-groups. An analysis of bulbar lesions in 114 patients showed that the 9th and 10th cranial nerves were most often affected, then the 3rd, 4th, and 6th nerves; the 8th nerve was least often involved. But here again the distribution differed widely with age. Medullary paralysis occurred in direct proportion to age, but generally speaking the frequency and severity of both spinal and bulbar types of the disease was greatest among young adults aged 16–30. This is reflected in the age-distribution of 20 fatal cases; no children up to 5 died, and when all children were compared with all adults the fatality-rate was nine times higher in the latter. McConnell's[4] experience in Northern Ireland in 1950 was very different: of 243 cases of poliomyelitis admitted to the Northern Ireland Fever Hospital in that year, 10 were paralytic cases in infants up to 6 months of age; and of these 3 died.

Poliomyelitis, as Burnet[5] has observed, "is a changing disease that has not yet reached a standardized expression." The gradual upward trend in age is ascribed by Weinstein et al. to the presence of strains of virus that are antigenically distinct from the Lansing strain, against which a large number of older children and adults have neutralising antibodies; and the absence of such antibodies against the newer viruses may explain the present trend. This, however, is certainly not the only factor in determining the age-distribution of this elusive disease. In Burnet's words: "Only some dynamic interpretation based upon the changing requirements for survival of a virus whose environment is being altered by its host species' changing social habits can give an adequate comprehension of the phenomena."

SPECIFICATIONS FOR FOOD

SOME would say that, where food purveyance is concerned, "they order it better in the United States." Certainly, the Americans have a Food and Drugs Administration which in some respects acts as that "national consultative assembly" of experts that both Mellanby and Coppock have advocated for this country. What is more, according to a report in the *New York Times* of May 15, the U.S. Administrator has now promulgated orders by which standards are prescribed for the bulk of the nation's bread—all this to "promote honesty and fair dealing in the interests of consumers." Five categories are recognised—white, enriched, milk, raisin, and whole wheat. For all of these the basic ingredients are specified, maximum moisture and minimum dry matter contents are laid down, certain ingredients—cottonseed flour, oat flour, and "many chemicals" (including polyoxyethylene monostearate and related compounds as "softeners")—are vetoed, and a full declaration of the miscellaneous ingredients by labelling is stipulated. The final form of these regulations has, moreover, been arrived at only after protracted public hearings. In future, then, the American staff of life is to be both genuine and trustworthy.

If this American course of action were pursued to its logical conclusion the result would be authoritative specifications for a whole host of food commodities. It is from this sort of positive legislation that the British, as though by contrast, have deliberately veered. Instead, we depend mainly on the honesty and social good sense of the interests concerned, and only when voluntary arrangements have been found lacking have restrictive

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1. Henderson, W. *Lancet*, Feb. 23, 1952, p. 386. Leading article, *Ibid*, p. 404.
2. Bradley, W. H., Gale, A. H. *Mon. Bull. Min. Hlth, P.H.L.S* 1948, 7, 56; *Ibid*, 1950, 9, 216, 242.
3. Weinstein, L., Shelokov, A., Seltser, R., Winchell, G. D. *New Engl. J. Med.* 1952, 246, 296.
4. McConnell, A. A. *Arch. Dis. Childh.* 1952, 27, 121.
5. Burnet, F. M. Virus as Organism. Cambridge, Mass., 1945; p. 63.

measures been taken. Thus it required the dramatic demonstration that nitrogen trichloride (agene) could produce running fits in dogs and other animals before the Government could be induced officially to discountenance its further use as a bleaching component in flour; and even then the directive was framed so as to come into force no sooner than material considerations allow. Meanwhile the discussion at the Royal Society of Medicine which we reported last week shows that far more effort is being put into the testing of substitutes like chlorine dioxide than was ever employed before agene was introduced in the first place.

Deplore it as we may, some degree of "sophistication" of foods has probably come to stay. Admittedly the reasons are largely economic, but a general return to the more natural products may not be feasible if our largely urbanised community is to count on having a regular supply of food, in season and out. Yet if we can take comfort from the fact that known examples of direct toxicity or harm from food-processing are few, we must nevertheless be constantly on the watch for possible evidence against the methods employed. Some of the utterances of food scientists are far from reassuring, and nobody with pharmacological recollections will be satisfied with such a statement as that "the amounts of chemical improver used are small." There are numerous examples of potent drugs acting on the body that do so in minute doses, and the pathology of various increasingly prevalent diseases is not yet so clear that we can rule out the possibility of undetected noxæ in contemporary food.

ANIMAL WELFARE IN THE UNITED STATES

WE have been exceptionally fortunate in the way our legislation for the protection of laboratory animals has matured; for it arose directly from the opinion of the scientists engaged in experiments requiring the use of animals. The British Association for the Advancement of Science resolved, as early as 1871, that no experiment which can be done with the animal under an anæsthetic should be done without it; that no painful experiment is justifiable for the mere purpose of illustrating a law or fact already demonstrated (i.e., such experiments should not be used in teaching); and that when, in order to obtain a new fact, it is necessary to cause pain, every effort should be made to ensure success, so that pain is not inflicted uselessly. These opinions, which provided the basis for the relevant sections in the Cruelty to Animals Act of 1876, are now reinforced by a growing conviction among research-workers that animals should not be used in large numbers for painful experiments when the facts can be established equally well by the use of a few. This reasonable and moderate approach to a difficult matter has put our scientists in a very strong position to meet the arguments of antivivisectionists. Moreover it has not hampered their work in any way: indeed they regard the legal requirements as a valuable safeguard of their interests.

In the United States the situation has developed along different lines. Angered by the attacks of antivivisectionists, members of the National Society for Medical Research are not only insisting on their right to be free of restrictions on animal experiment, but are going farther and launching an attack on their opponents. This has taken the form of applying, in several States, for legislation compelling animal welfare organisations to hand over, for experiment, stray animals brought to their animal-pounds for humane care or destruction; and in some States such legislation has already been passed and is now in force. This has had the effect of shaking the confidence of ordinary people in the purpose and integrity of such organisations; and some voluntary bodies have thought it better to close down rather than become procurers of animals for experiment. Such a Bill is now pending in the New York State Assembly, and if passed will make it a misdemeanour to harbour a stray animal without reporting to a designated authority within 24 hours.

In an attempt to offer a more temperate and constructive programme, a group of interested people—including Dr. Lee R. Dice, director of the institute of human biology, and Dr. Robert Gesell, professor of physiology, in the University of Michigan—have formed a new Animal Welfare Institute (A.W.I.) to promote the welfare of all animals and to reduce the total of fear and pain inflicted on animals by man. Like our own Universities Federation for Animal Welfare (UFAW), members of this body are not opposed to animal experiments but merely wish to ensure, as far as possible, that the ultimate value of any such experiment justifies the pain inflicted, that the feasibility of other, less painful, methods is always considered, and that laboratory animals are not subjected unnecessarily to fear, discomfort, or loneliness. They are anxious to work, as UFAW does, in coöperation with research-workers, but they have been hampered at the outset by a demand of the New York State Society for Medical Research that they should "unreservedly back" an animal-pound Bill of the type described. This, of course, the A.W.I. are not able to do; for while it is one thing to accept that stray animals brought to a public pound may reasonably be used for research, it is quite another to agree that a welfare society, formed to satisfy a different purpose, and supported for that end by voluntary subscriptions, should be diverted to uses which its sponsors have not selected and of which they may strongly disapprove.

The new institute is therefore being attacked both by the antivivisectionists, because it does not condemn animal experiments, and by the research scientists, because it does not approve their policy towards animal welfare societies. This opposition to a middle course seems as remarkable to us as the assertion in one of the letters sent to the A.W.I., that "the great majority of experimental biologists and medical research investigators do not want the counterpart of the laws and regulations that the English have imposed, and are entirely behind the Medical Research Pound Bill pending in the New York State Assembly." Every country must work out its own ethic in cases like this; and there is every reason to believe that individual research-workers in America impose on themselves a code of humane regard for animals every bit as stringent as that accepted here. Regulations are designed not for well-doers, however, but for the aberrant; and, mankind being what it is, these are as likely to be found among research scientists as any other group. Dispassionate consideration of principles should convince our American research colleagues that if they are going to insist on freedom for themselves from restrictions imposed from without they should, in common fairness, insist equally on freedom from similar restrictions for the animal welfare societies. For, after all, the broad aim of these societies is identical with that of medicine—they are merely more catholic in their choice of the animals they befriend. Moreover, if American scientists cannot tolerate restrictions imposed from without they can counter antivivisectionist propaganda in another way—by drawing up their own code of humane behaviour and requiring members of their scientific bodies to conform to it.

Meanwhile those interested in the care of laboratory animals will wish the newly founded Animal Welfare Institute well; and some may feel inclined to forward its work by becoming members. The address of the institute is 730, Fifth Avenue, New York, 19, N.Y., but Mrs. Christine Stevens, the president, is at present over here, staying at Grosvenor House, Park Lane, London, W.1, and would welcome inquiries.

Special Articles

APPOINTMENT SYSTEMS IN HOSPITAL OUTPATIENT DEPARTMENTS *

J. D. Welch
BRIGADIER, RETD; MEMBER OF TEAM INVESTIGATING FUNCTIONS AND DESIGN OF HOSPITALS (NUFFIELD PROVINCIAL HOSPITALS TRUST AND UNIVERSITY OF BRISTOL)

Norman T. J. Bailey
M.A. Camb.
STATISTICIAN TO THE MEDICAL SCHOOL, UNIVERSITY OF CAMBRIDGE

Although very many hospitals now use some kind of appointment system for outpatients, anybody entering the waiting-rooms of most outpatient departments will at once be impressed by the large number of people waiting. It is not uncommon to find that patients are there for over an hour before being seen by the doctor with whom they have an appointment. During much of that time many just sit, often under conditions which do not permit the time being usefully or even pleasantly occupied. To keep patients waiting longer than is really necessary is clearly undesirable on humanitarian grounds, and moreover often means a loss of working time which the country can ill afford. Some patients are on sick-leave, but others take a half or even a whole day off work because a visit to the hospital lasts so unpredictably long. Again, a large number of people collected together requires large waiting-rooms which, in the present shortage of hospital accommodation, could be used more profitably.

This state of affairs has arisen because it has always been considered overridingly important to ensure that the time of consultants is never wasted. We do not propose to discuss the rightness or otherwise of this view, but rather to show how an appointment system can be used to save the time of the patient without wasting the time of the consultant.

TABLE I—PUNCTUALITY OF PATIENTS

Clinic	No. of patients	Average no. of minutes		Average waiting time (min.)
		Early	Late	
Gastric	185	8	..	35
Anæmia	83	16	..	65
Chest	87	13	..	43
Diabetic..	81	6	..	41
General medical ..	80	11	..	69
Daily dressings ..	338	..	13	69
Varicose veins	132	..	8	73
Infected hands ..	66	0	0	32
Neurosurgery	84	4	..	85
Surgical	188	1	..	68
Rectal	102	..	3	80
Surgical	144	..	3	50
Surgical	213	3	..	75
Surgical	168	2	..	73
Surgical	146	5	..	93
Skin	883	8	..	67
General medical ..	231	10	..	49
General medical ..	61	14	..	74
Ophthalmic	246	10	..	29
E.N.T.	144	11	..	60
Pædiatric	147	..	3	65
Skin	110	6	..	46
Obstetric	135	..	6	95
General surgical ..	240	10	..	37
Gynæcological ..	85	12	..	46
Radiotherapy	219	15	..	31
Obstetric	170	20	..	93
Obstetric	145	21	..	63
Dressings	398	0	0	42
O.P. dressings	353	11	..	38
Fracture	219	14	..	16
Diabetic	171	9	..	63
Chest	69	1	..	23
Orthopædic	130	14	..	35

The two main factors which affect the design of an appointment system are punctuality and consulting time.

PUNCTUALITY

To find out whether patients were punctual for their appointments, time studies were taken in 2 teaching and 7 non-teaching hospitals, covering 34 clinics. As patients entered the outpatient department they were given a card or a number, and independent observers with synchronised stop-watches recorded the progress of patients, including details such as their appointment time, the time of their arrival, and the time at which consultation began. The punctuality of these patients is shown in table I.

It will be seen that at only 6 clinics out of the 34 were patients on average late for their appointments. At all other clinics except 2, patients were on average early, sometimes by quite an appreciable period of time. Thus as a body patients are not late: some are late, but most of them are early. This conclusion was also reached by Dale (1951) at the Children's Hospital, Sydenham.

TABLE II—PUNCTUALITY OF CUSTOMERS

Establishments	No. of customers	Average no. of minutes		Average waiting time (min.)
		Early	Late	
A	199	..	0·26	5·00
B	214	1·24	..	2·40
C	248	0·52	..	3·30
D	277	1·24	..	3·48

Now, satisfactory as was the punctuality of most patients, there were some patients who were very early. The usual reason given for turning up very early is "So as to get to the head of the queue." A search was made for a clinic which achieved real punctuality, shown by only slight variations from appointment times; where patients were kept waiting only a few minutes and were always seen in accordance with their appointments and not necessarily in the sequence of their times of arrival. But no such clinic could be found. Accordingly, we turned our attention to commercial establishments in an attempt to find an efficient appointment system really producing punctuality. Ladies' hairdressing establishments provided what was required. Here the time that is taken for "treatments" is known. Customers are not allowed to have extra "treatments" done; since if they did, it would upset the appointments of others. Discipline of both staff and customers is strict. The punctuality of customers in some of these hairdressing establishments, none of which was of the exclusive Mayfair brand, is shown in table II.

The contrast between tables I and II is striking. It is not reasonable to carry this comparison too far, since the problems of the hospitals are much more complicated than those of the hairdressers. The variable time of the consultation is only one of the greater difficulties with which hospitals have to contend. Nevertheless, table II shows how punctual people can be when strict time discipline is imposed. Even if hospital outpatient clinics cannot reduce their waiting time to as low a figure as the hairdressers, they can at least improve their record.

But the punctuality of patients is only one side of the keeping of an appointment. It is also up to the medical staff themselves to be punctual for the start of their clinics. Their punctuality is shown in table III.

With exceptions, the medical staff of hospitals make little attempt to be punctual. They do not realise that at present every minute that they are late causes the same increase in waiting for *every* patient. There are a variety of reasons for this late arrival, but the over-

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* This study was undertaken as part of the Investigation into the Function and Design of Hospitals sponsored by the Nuffield Provincial Hospitals Trust and the University of Bristol.

TABLE III—PUNCTUALITY OF MEDICAL STAFF

Clinic	No. of medical staff	Average no. of minutes	
		Early	Late
Gastric	15	..	8
Anæmia	6	..	10
Chest	9	..	29
Diabetic	4	..	14
General medical	6	..	37
Daily dressing	4	..	9
Varicose veins	3	..	14
Infected hands..	3	..	14
Neurosurgery	2	..	14
Surgical..	3	..	11
Rectal	1	..	14
Surgical..	7	..	23
Surgical..	9	2	..
Surgical..	5	..	8
Surgical..	4	..	16
Skin	20	..	19

riding one is traditional. They have grown accustomed to seeing patients waiting. As the Department of Health for Scotland (1952) puts it, "The efficient working of many departments is hampered by a tradition based on attendance of voluntary medical staff for restricted hours." The importance of punctuality was recognised as long ago as 1908 when Osler, opening the new outpatient department at Cardiff Infirmary, said:

> "As one who has had a long hospital experience, may I mention one essential virtue for the members of the outpatient departments staff to cultivate—namely, punctuality. It is not, of course, always possible but it is remarkable how greatly it facilitates the work of an institution when men put in an appearance at the stroke of the hour."

If the medical staff were always punctual for the start of their clinics, an important step would be taken towards making outpatient departments more humane and more efficient. There need be no fears about the punctuality of the nurses: they are always on duty preparing the rooms, often some time before each clinic is due to begin.

LENGTH OF CONSULTATION

If the late arrival of the medical staff is one of the reasons why patients have to wait a long time, it is clear from a comparison of tables I and III that it cannot be the only cause. The clinics shown in table III are the same as the upper 16 in table I. Thus in the first clinic the average time for which patients had to wait was 35 minutes; but the lateness of the medical staff only accounted for 8 minutes. There is in fact no clinic in which the waiting time of patients can be wholly attributed to the lateness of the medical staff. The reason is not far to seek. Patients are called at a rate in excess of that at which the medical staff can clear them. This is a feature common to most systems and is a great cause of excessive waiting. It is inherent in any system which does not attempt anything more accurate than is implied by such appointment systems as:

15 patients at 1.30 P.M. (for a 2 P.M. clinic) and thereafter 10 at 2.15 P.M. and 10 at 2.45 P.M.
10 patients per half-hour.
4 patients per half-hour.
3 patients every 15 minutes.

The average time that the patients have to wait before they are seen is about one hour (table I). If it is borne in mind that there are 26 million outpatient attendances in England alone during a year, then the waste of time—a lot of it *working* time—may be imagined. This waste cannot be reduced except by calling patients more in accordance with the rate at which they can be cleared. This means studying in detail the actual consultation times of doctors.

The total length of a consultation—which covers history-taking, examination, and advice, and often a certain amount of undressing—is a variable quantity: it can be anything from a few seconds to, say, half an hour. But if one examines the consultation time of a large number of patients a certain statistical regularity emerges. Although it is entirely up to the consultant to decide how long he spends with a given patient, the frequency distribution of a large number of consultation times may be highly characteristic of a particular class of patient. Bailey (1952) found that, for general surgical and dermatological patients at least, the length of consultation times followed a well-defined pattern which was satisfactorily fitted by what is known, mathematically, as a Pearson type III distribution (fig. 1).

When their times per patient are presented in this way doctors will readily agree that in most clinics they have a few patients who only take a short time, many more who take a minute or two, and usually one or two who need lengthy consultation and/or examination.

THE MATHEMATICAL THEORY OF QUEUES

A considerable amount of work has been done in the past on the mathematical theory of queues. As a rule it has been found necessary to simplify the practical problems so that theoretical treatment becomes possible. The best recent introduction to the statistical theory of queues is the paper by D. G. Kendall (1951) which has an extensive bibliography. Kendall was chiefly concerned with queues fed by a random input, whereas with a queue controlled by a well-designed appointment system arrivals would occur regularly at predetermined intervals. Further theoretical progress has been made by Lindley (1952) who has found the limiting distribution of patients' waiting times for infinitely long queues when the appointment interval is greater than the average consultation time. But this is still too remote for practical application to our problem.

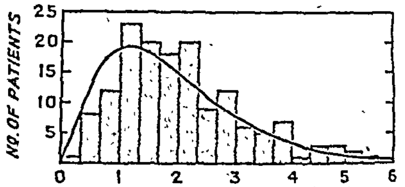

Fig. 1—Frequency distribution of 151 consultation times.

A somewhat different approach to the difficulties of dealing with short queues has been made by one of us (Bailey 1952).

Having established that consulting times varied in the way that has been described, he created a whole series of hypothetical consultation times. A table of random numbers was used for selecting times from the theoretical distribution. A series of 25 such times was then regarded as a typical example of what might occur in practice with 25 patients attending a single clinic. For any given appointment system, the length of time that the consultant spent with each patient, how long the patient waited, and the size of the queue in the waiting-room could be calculated by means of tedious but straightforward arithmetic. In this way 50 clinics each of 25 patients were constructed and the progress of patient and consultant was recorded. The work was laborious but this number of clinics was necessary to ensure that the considerable variations in consultation times were adequately covered.

Bailey examined the consequence of the consultant starting his clinic with 1, 2, 3, &c., patients present and also the effect of varying the length of the appointment interval relative to the average consultation time. Suppose that, for clinics of 25 patients with an average consultation time of 5 minutes, a quite arbitrary figure, the appointment interval is exactly 5 minutes. Then, for the simplified type of situation under discussion, it was shown that if the consultant were to waste *only* about 30 seconds on average per clinic he should start his clinic with 6 patients present, the patients waiting on average 27 minutes each. On the other hand if he started with only 1 patient present he would waste on average about 9½ minutes a clinic, while the patients' average waiting time would be reduced to about 7½ minutes. The average waiting time for patients and the corresponding total idle time for doctors follow a clearly defined curve dependent upon the number of patients present when the clinic begins (fig. 2).

That a consultant's time is more valuable than a patient's is a view which is generally acceptable to the lay public as well as to the medical profession. Nevertheless, the consultant's time is not infinitely valuable, and in practice some kind of a balance must be struck between doctor and patient. This is especially true when one considers the industrial working time lost by patients staying away from work to attend a clinic.

A reasonable balance would, we believe, be struck by giving patients appointments at an interval equal to the average consultation time, and starting each clinic with 2 patients present. Patients would then wait on average 9 minutes after their appointments, or the equivalent of 225 minutes' total waiting by the 25 patients of a single clinic. This may well be judged sufficient when set against the consultant's average idle period of certainly less than 6 minutes per clinic, allowing for patients arriving early. The present average wait of 60 minutes (table I) shows how much doctors are over-insuring themselves against being kept waiting during a clinic.

Bailey showed that the appointment system is rather sensitive to changes in the appointment interval. If a consultant started his clinic with 2 patients present, a 10% increase in the appointment interval would double the consultant's average idle period, while a 20% increase would make it 3½ times as long. Reductions in the appointment interval reduce the consultant's wasted time but increase the patients' waiting time, though this effect is not quite so critical. Thus it is important to assess the average consultation time accurately, and for this purpose as many as 400 actual measurements of time per patient are probably necessary. Alternatively some doctors might find it easier to time themselves over a sample of, say, 100 patients, and modify their appointment system later if their first calculations turn out to have been based on too small a sample.

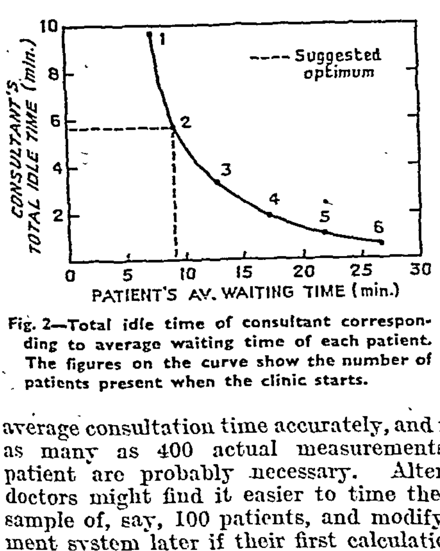

Fig. 2—Total idle time of consultant corresponding to average waiting time of each patient. The figures on the curve show the number of patients present when the clinic starts.

PRACTICAL RECOMMENDATIONS

Although arguments about the consequences of various kinds of appointment systems are unreliable when based on *average* consultation times and not on an analysis taking into account the full range of variation, the theoretical work we have briefly reviewed shows that considerable insight into the working of an appointment system is possible. Of course the simplicity of a theoretical formulation is bound to be disturbed by practical complications.

Separation of Groups of Patients with Different Average Consultation Times

If old patients had one fixed consultation time and new patients a different fixed consultation time, then some waiting would be inevitable unless the two types of patients were kept separate, each having their own clinic with an appointment interval equal to the appropriate consultation time. Similar considerations apply when there is a statistical distribution of consultation time. If the average consultation times for old and new patients are different, as is usual, then it is more efficient to design separate appointment systems for the two types of patients. As a general principle, any class of patient with an average consultation time which is appreciably different from that of other classes should be dealt with on its own. If there are too few patients for a whole clinic then the first part of the clinic might be confined to new patients who would be called forward at the rate appropriate to their average consultation time, while the second part of the clinic would be confined to old patients with a different appointment interval. In many hospitals this is already done.

Need for Efficient Routine Working of Clinic

If the expected saving of waiting time is to be realised, the general routine of the clinic must be efficient. Any shortcomings in the secretarial work—such as undue time spent in finding records—will prevent optimum working. The best solution seems to be the employment of a secretary-receptionist who can always attend the clinics of her particular consultant or consultants. She should draw the case-papers beforehand from the records department and have them ready. She should shepherd the patients in and out of the consulting-room ; and with each of them who needs a further visit she should fix a suitable appointment time.

Punctuality of Patients and Consultants

The punctuality of both patients and consultants has already been discussed. On the whole patients are early. They should perhaps be restrained from being excessively early, for this leads to undesirable overcrowding of waiting-rooms. On the other hand a reasonable degree of earliness has the important, though somewhat incalculable, consequence of reducing the consultant's idle period. Thus the average time actually wasted per clinic by the consultant is likely to be less than 6 minutes predicted under the conditions assumed. Again, if most patients are early the effect of a patient being occasionally late or failing to turn up will be largely offset.

If the consultant is not on time the success of the scheme may be completely vitiated. The figures given earlier (assuming an average consultation time and appointment interval of 5 minutes each) showed that if the consultant started his clinic with 2 patients present, the patients average waiting time would be about 9 minutes. If the consultant arrived 20 minutes late, when there would be 6 patients present, the patients' average waiting time would rise to 27 minutes.

Diagnostic Tests

If a consultant wishes to have some diagnostic test made before resuming his examination of a patient, then all the time that the patient is with the doctor—but *not* the time during which the diagnostic test is being made—should be included in the consultation time for that patient. It is often this kind of patient whose consultation time creates the tail of the Pearson type III curve.

Rest for Consultant During Clinic

Many consultants welcome a break in the middle of a session for refreshment and discussion with colleagues. Where this is the established practice the appointment system should be suitably modified. If patients continue to arrive during the break, the average waiting time of patients seen after the break will be considerable. The simplest solution is to treat the two parts of the clinic as entirely separate. Thus patients can be given appointments at regular intervals from say 10 A.M. to 11 A.M. Consultation with the last patient in this series would probably end at about 11.15 A.M. The first appointment for the second part of the clinic might be made for

11.45 A.M., and the consultant would recommence work at 11.50 A.M.

Waiting-rooms

With a good appointment system the number of patients in the waiting-room at any instant should be greatly reduced. In a special case studied by Bailey (a clinic of 25 patients with average consultation time and appointment interval each 5 minutes; consultant starting with 2 patients present) the waiting-room would be empty 22% of the time; 86% of the time it would contain fewer than 4 patients; and for only 2% of the time would there be more than 5. If, however, all patients were 10 minutes early, then there would be fewer than 3 patients in it for 22%, fewer than 6 for 86%, while for only 2% of the time would there be more than 7 patients waiting.

Number of Patients Seen per Clinic

Although most of Bailey's (1952) results were expressed with reference to an average consultation time of 5 minutes, this was done only to make the practical implications easier to grasp. Indeed a table was given showing the patients' average waiting time and consultant's average wasted time per clinic for clinics of 10, 15, 20, or 25 patients with average consultation times of $12^{1}/_{2}$, $8^{1}/_{3}$, $6^{1}/_{4}$, and 5 minutes respectively. These values were chosen so as to make each clinic last about 2 hours 10 minutes. The actual average waiting times showed some variation, but the general conclusions as to the best type of appointment system remained unaffected. By suitably scaling the results given, predictions can be made about a wide range of alternative average consultation times and different numbers of patients seen per clinic.

Exceptionally Long Consultations

It sometimes happens that a consultant decides to seek a second opinion from a colleague. Such contingencies may give rise to an occasional very long consultation time. If this occurs more often than is allowed for, then the patients' average waiting time will be increased but the consultant's idle period will be reduced. One cannot always avoid this kind of situation, but where possible very long consultations should be postponed to the end of the clinic.

SUMMARY

Investigations have shown that patients are usually early rather than late. There is reason to think that, when clinics are run efficiently, patients will get nearer to being punctual.

There is plenty of evidence that doctors, on the whole, are late for their clinics. If they could be punctual a first and important step would have been taken towards making clinics more civilised as well as more efficient.

There is a close relation between the length of time for which patients wait and the total idle time of doctors in a clinic. At present doctors are over-insuring against ever being kept waiting. This over-insurance is at the expense of the patient. By being prepared to wait occasionally for a very few minutes, doctors could enormously reduce the length of time that patients have to wait.

It is suggested that each doctor, if he does not already know it, should ascertain his average consultation time for each type of clinic he holds. In working this out he should include all time spent on consultation, examination, entering up case-papers, &c.—in short, everything he does for the patients. He should exclude time taken up by casual interruptions. The total time calculated in this way to the nearest minute, over a number of the same kind of clinics, should be divided by the number of patients seen, which should not be less than, say, 100. The resultant average consultation time per patient will determine the interval at which each patient should be given his appointment. To prevent excessive waiting for the doctor, each clinic should begin when 2 patients are present.

Old and new patients, or other particular categories, should be seen in separate clinics or at separate times in the same clinic.

If the consultant prefers to run his clinic with a rest-break in the middle it is preferable to regard this as dividing the session into two clinics and to adjust the appointment system accordingly.

REFERENCES

Bailey, N. T. J. (1952) Study of Queues and Appointment Systems in Outpatient Departments, with Special Reference to Waiting-times. *J. R. statist. Soc.* A, 14 (in the press).

Dale, A. C. (1951) *Hospital*, 47, 569.

Department of Health for Scotland (1952) Interim Report on Hospital Planning. In the press.

Kendall, D. G. (1951) Some Problems in the Theory of Queues. *J. R. statist. Soc.* B, 13 (in the press).

Lindley, D. V. (1952) The Theory of Queues with a Single Server. *Proc. Camb. phil. Soc.* 48, 277.

Osler, W. (1908) *Brit. med. J.* i, 1470.

THE NEW CHARGES

By regulations under the National Health Service Amendment Act, 1949, and the National Health Service Act, 1952, new charges will be introduced on Sunday, June 1, for medicines, dressings, and appliances prescribed by general practitioners, for medicines and certain appliances obtained through hospital outpatient departments, for dental treatment, and in connection with day-nurseries run by local health authorities.

GENERAL PRACTITIONERS' PRESCRIPTIONS

A charge of 1*s.* for drugs or dressings will be made as follows:

1. In respect of an item or items ordered on any one form E.C.10, E.C.10H.P., or E.C.14, and supplied by a chemist-contractor.
2. In respect of an item or items supplied by a dispensing doctor on any one occasion.

The 1*s.* charge will not be payable if any of the following elastic appliances (with charges in parentheses) are ordered on the prescription form or supplied by the doctor on the same occasion:

Anklet, kneecap, legging, thigh piece (5s. each); knee legging, stocking, thigh kneecap, knee stocking, thigh legging, thigh stocking (10s. each).

Repayment can be obtained by the following: (*a*) people receiving National Assistance and their dependants, (*b*) war pensioners where the prescription is needed because of accepted war disabilities; (*c*) others who establish a claim of hardship with the National Assistance Board.

Chemist-contractors will normally collect the charges in cash and retain them, their remuneration being adjusted accordingly. In rural areas, however, chemist-contractors who may be unable to collect a substantial proportion of the 1*s.* charges in cash may, with the agreement of the executive council, accept postage stamps, to be affixed to the prescription form; and in this event no deduction will be made from remuneration. Normally an allowance of $\frac{1}{4}$*d.* per form will be made to cover cases in which the contractor may be unable to collect the 1*s.* charge; but for the rural chemist who is allowed to surrender stamped forms the allowance will be $\frac{3}{4}$*d.* on each form, stamped or unstamped.

Dispensing doctors will collect the 1*s.* charge either in cash or in stamps, converting all payments to stamps. No deduction will be made from dispensing doctors' remuneration in respect of the 1*s.* charge. "It is expected hat doctors will do their best to collect charges due, nd it has been agreed that Local Medical Committees will review any cases put before them in which collection ppears to be inadequate."

PRESCRIPTIONS IN OUTPATIENT DEPARTMENTS

A charge of 1*s*. will be made to outpatients (but not npatients) each time that drugs are dispensed to them, with the following exempted: (*a*) patients receiving National Assistance or their dependants; (*b*) war pensioners receiving medicines for their accepted disability; and (*c*) patients attending venereal-disease clinics who receive the medicines as part of their treatment. Others who wish to claim repayment on the ground of hardship should apply to the National Assistance Board.

For appliances the charges will be as follows: elastic hosiery, 5*s*. or 10*s*. each; surgical abdominal supports, £1 each; surgical footwear, £3 a pair (repairs, 1*s*. 6*d*. for heeling to 13*s*. 6*d*. for complete long-soling); wigs £2 10*s*. each. There will be no charge where the appliance is supplied to a child under 16 or in full-time attendance at school; to people receiving National Assistance or their dependants; to war pensioners in respect of their accepted war disabilities; or to people who are inpatients when the appliance is supplied. No charge will be made for appliances prescribed or ordered for any patient before June 1. Patients to whom the payment of these charges causes real hardship can apply to the National Assistance Board for help.

AMENITY BEDS IN HOSPITALS

The charges for amenity beds will now be: single room, half the cost up to 12*s*. a day; small ward, quarter of the cost up to 6*s*. a day.

DENTAL TREATMENT

There will be a charge of £1 or the full cost of any treatment if less than £1. The charges for dentures—up to £4 5*s*. for a full upper and lower denture—will continue to apply; but if a patient receives dental treatment including the supply of full dentures, the total charge will not exceed £4 5*s*. In future the charge for dentures will also apply to bridges.

The charges will apply to any patient where the first examination takes place on or after June 1. No charge will be made for clinical examination of the mouth; nor will a patient be required to pay for treatment for arrest of bleeding or for any domiciliary visit up to five miles. Repairs to dentures will remain free.

Charges for treatment, other than the supply or relining of dentures, will not be made in the case of anyone under 21 years of age, or of expectant mothers or mothers who have given birth to a child during the preceding twelve months. The new charges will also not apply to treatment given at a hospital to inpatients or outpatients. Those wishing to claim repayment on the ground of hardship should apply to the National Assistance Board.

DAY-NURSERIES

Power is now given to local health authorities to make charges for the use of day-nurseries, relating these charges to the actual cost and to the means of the parents.

THE REGISTRAR PROBLEM

THE Council of the Registrars' Group of the British Medical Association met on May 1 to consider the position of its members in the light of the recent letter from the chief medical officer of the Ministry of Health [1] to the Joint Consultants' Committee. The lack of information on the size of the problem and the negative attitude of the Ministry caused considerable anxiety.

The executive of the Registrars' Group have, since this letter was received, gathered as much information as possible about the number of senior registrars affected. From the information obtained from ten regions, it seems that at least 175 senior registrars occupy posts which will no longer be established and are in danger of dismissal before October, 1952.

It is evident that there is need for a revised senior registrar establishment. It is not felt, however, that any plan is fair that fails to recognise the special position of the post-war generation of senior registrars and proposes a precipitate reduction of posts. Such an immediate reduction would release on to the medical "labour market" a flood of doctors whose chances of immediate re-employment would be small. The Danckwerts award and other long-term plans will eventually improve the position as regards entry into general practice, but these cannot affect the immediate issue.

The executive of the Registrars' Group are preparing a memorandum for discussion with the Joint Committee. This will advocate, in general, a method of "running down" the establishments slowly in a way which will give the fairest possible treatment to the senior registrars and registrars concerned.

The effective remedy still seems to be extension of the number of consultant posts; for obviously when the senior registrars are "axed" greater work will be thrown on the present consultants, and on the intermediate registrars who are not yet qualified by experience to undertake it.

R. M. F.

The Wider World

IN FINLAND

To me, Finland is essentially Scandinavian, despite the fact that only 9% of her 4 million inhabitants speak Swedish (and one of them is my wife). Finland was united to Sweden from 1154 to 1809, and even after Russia annexed the country as a Grand Duchy in 1809 the Swedes remained and with them their influence. In 1918 Finland became independent and the nationalism of the Finns tended to oust the Swedes from their somewhat privileged position. All the world knows that patriotism rose to a new height in the winter of 1939–40 and again in 1941–44; but perhaps it is less well recognised that peace called for many sacrifices which were borne in a new spirit of good will.

An eighth of Finland was ceded to the Soviet Union and this rendered 500,000 homeless, for the number of Finns who accepted Soviet citizenship was negligible. The problem was solved by making a law that nobody should have a house or flat with more rooms than there were occupants. "One person, one room" works well. For example, a family of a husband, his wife, a maid (not a luxury, for his wife is a dental surgeon), and his three children aged 6, 4, and $1^1/_2$ have a large sitting-room, a fairly large dining-room, the parental bedroom, one for the maid, one for the children, and a large kitchen, which counts as a sixth because it is more than 15 sq. metres. Small flats have their compensations and make god-nigh cleanliness possible. It was difficult to imagine that flats over shops could be so elegant (to borrow an Americanism). The absence of coal fires makes them easy to keep clean.

Another feather in Finland's cap is her discharge of reparations. The Finns boast that theirs was the only country which repaid the Americans after the 1914–18 war, and to show their appreciation the U.S.A. have converted these payments into scholarships (chiefly medical) for Finns to visit America. In a few months' time they will have repaid the U.S.S.R. 226·5 million dollars' worth of goods valued at 1938 prices, despite Finland's losing 13% of her industrial capacity and 32% of her power-stations in the ceded areas, together with all the German-owned factories, shares, and houses, which were taken by the Russians.

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[1] See *Lancet*, May 24, 1952, p. 1061.

How is it done? Wood in various guises is the chief export. In 1950 wood products were 44%, pulp 23%, paper and cardboard 20%, and other goods 13%. Those who complain that the *Times* has been forced to go up to 4*d*. from 3*d*. will find little consolation in knowing that English coal, which was 1000 marks (about 30s.) a ton before the war, is now about 10,000, though the Government subsidy keeps it at about 6000 or £10 a ton. "How is it in England?" was qualified as soon as asked, with the phrase, "Good, I hope, because when it is good in England, it is good here." Almost a quarter of Finnish exports and imports are to and from Great Britain—and the Soviet Union is second with 10%. This is a great difference from pre-war days when Germany did the biggest trade.

One result of the late war is that English is now taught more often in schools. The linguistic feats of the Finns are well illustrated by a Saturday morning demonstration in Helsinki. Professor Yllpö asked me the previous evening to come to the weekly demonstration which he said they would conduct in "slow English." This started punctually at 10, when the pathologist demonstrated post-mortem specimens to illustrate leukæmia and cerebral abscess, the radiologist a case of congenital œsophageal atresia complicated by pyloric stenosis, the assistant physician and a house-physician several other cases—everything being discussed by the surgeon, the professor, and the other assistants and listened to by some forty students. All was in English with an occasional aside in Finnish. Some spoke better than others, but all were adequate, and the laughter of the students at appropriate moments showed that they followed the proceedings. Necessity is largely the mother of this facility, for Finnish and Swedish are not among the twenty-two languages which are spoken by over 20 million people. As the professor said later, "If I speak Swedish 10 million understand me; if I speak German 100 million, or Russian 120 million; but if I speak English, 200 million understand me."

Diet is undoubtedly responsible for variation of disease in Sweden and Finland. *Smörgåsbord* has to be seen to be comprehended, and much of the food is first-class protein—pork, and fish in their various forms, and delicacies requiring an acquired taste, like reindeer. The profit of this high-protein and high-fat diet is a low incidence of permanent liver damage despite the consumption of large quantities of alcohol and a fairly high prevalence of infective hepatitis: the loss is the large number of people in the twenties with gallstones. Vegetables are rarely eaten ("we don't like them") and anæmia is very common. Much eating of fresh-water fish makes Finland the research centre for dibothriocephalus anæmia, which they have recently shown to be due to the parasite's absorption of very large quantities of vitamin B_{12}: it seems that if the dry powdered worm is administered orally the anæmia is rapidly cured. The other disease which is fairly common is rickets, especially in parts of Finland too inaccessible to have the equivalent of child-welfare centres.

So I came back realising that Scandinavia still has a great influence in our life. Small countries provide eponyms such as Meulengracht's diet, Hagedorn's insulin, Waterhouse-Friderichsen syndrome, and Letterer-Siwe disease. In England we are never far from evidence of former Scandinavian associations, whether it is the Jenny Lind Hospital at Norwich in my native county or the numerous "by's" on the east side of Watling Street, such as Rugby (originally Rokeby), Kilsby, and Ashby St. Ledgers, to name three within ten miles of each other which were villages founded and named by the Danes. And as I look from my garden across a field to a row of wooden prefab houses built after the war, and called "Little Sweden," I have a constant reminder that wood is an essential of Swedish and Finnish prosperity.

R. E. Smith.

In England Now

A Running Commentary by Peripatetic Correspondents

FALLING asleep in a deck-chair I dreamed that I was looking in at the annual general meeting of a group of hospitals. When I arrived the chairman was delivering his review of the work during the year. "Our output of minutes and forms has broken all records," he said. Everyone clapped in approval. Turning to structural alterations, the chairman said that he was proud to report that the medical records department is now accommodated in one of the surgical wards to make room for the increasing staff and that it was hoped to find alternative accommodation for the patients. Everyone clapped again. "But," continued the chairman, "we are not spending the money unnecessarily. We are sparing no expense to effect economy. In fact if it had not been for the patients we could have a most efficient administration." Again everyone clapped.

On waking I told my dream to a friend. "That wasn't a dream," he said.

* * *

It recently became clear to us that humanity would be benefited if we could procure a bat to further our researches (a *fledermaus*, not a willow one), so we set about getting one. We know a zoologist who lives in the wilds—in one of those places where a single full-throated "Ar" is a strenuous evening's conversation—and arrives at the lab. with burrs sticking to his trousers. He had lately obtained a green lizard for one o our colleagues; the very man, we said, to get u a bat.

He proved unexpectedly diffident; he was not, i seemed, that sort of zoologist. "How do I catch them?" he said. We explained that all he had to do was lure th bat into a room and play to it a record of the ultrasoni squeaks of other bats, thereby upsetting its echo-soundin apparatus and causing it to collide with the chandelie and fall senseless to the ground; we had read it up He was still not convinced. "Where do I get the record?" he asked feebly. "My dear chap," we said, "don' bother us with details: buy a Galton whistle, as your air-raid warden, use a butterfly net, what d we care?"

All this was some time ago, and we still have no bat We see the zoologist now and then, but the affair marches badly—the bats fly too high for him, he says. "Well," we replied impatiently, "get us a wate bat then; they fly only a few feet up." He has no water it seems. We have suggested a tour of the neighbourin belfries, but he is a Nonconformist zoologist, on poo terms with the local High Church vicars. There are n caves in his district either. "What about barns?" we said, "England is an agricultural country, isn't it?" (By this time we were rather bitter.) But it is no good his heart is not in it. "Too wet for them to fly," h muttered sullenly when we passed him in a corridor th other day. We have tried rehearsing to him a night w once spent in the jungle in the middle of a rookery o several thousand flying foxes, and telling him of Cambridge undergraduate who collected college bats fo dissection. But he isn't shamed. "You can't expect the to come out this bright sunny weather," he told u yesterday.

Does anyone need a green lizard? We know zoologist who could get him one.

* * *

Our trip to the Netherlands coincided with the newspaper announcements of the arbitration award, wit their headings of "*£40 million for N.H.S. Doctors*" and the like. So it was perhaps excusable in some of ou acquaintances to greet our excited chatter about th proposed visit rather coldly. "Aha," one could see the thinking, "they're beginning on our 40 million alread We know the world. You can't fool us." The bette informed reader will be confident that my daughter an I were making the trip entirely on my husband's hard earned savings, and so were grateful for the respite fro such envious comment. Besides which, the Dutch being familiar with real suffering, were just the folk to raise our spirits. They did not fail us.

When we started to look about us, we noted first that the old and infirm in Holland do not keep worrying their doctors. They buy a St. Bernard dog and a folding stool, and play some simple musical instrument to cheer their fellow men, halting and feeble though the tunes may be, while the dog sits at their feet, bearing on its back a slotted tin labelled "*For the Music.*" They can leave the rest to the dog—those great tragic eyes will move the stoniest passer-by. And when coins go jingling merrily into the tin a great shaggy paw is lifted in acknowledgment. These old people are not beggars; they and their huge companions are part of the colour and sound of Amsterdam, that most colourful and tuneful of cities.

We remembered buying our first surgical instruments after the war in the company of a Dutch army doctor who was returning to help rehabilitate his shattered country. The process seems to be succeeding. We saw the whitest hospital curtains ever beheld in the heart of a great centre.

We can't build canals in *our* main towns, but is there anything to prevent our singing in the streets or as we go about our work? The Dutch have had as tough a struggle and still face as great difficulties and as crippling taxation; yet they are purposeful, hopeful—and cheerful. I asked one of their "dangerous intellectuals," whom the Nazis had put in a hostage camp, how they managed to keep so happy. He replied: "Holland has a long history. We have had an occupation. Now we are free again and it is good to be our own masters." The simple war memorial in the Dam sums up the answer in its inscription: "The Spirit Triumphs."

If the gloom doesn't lift in our green and gracious homeland I shall buy me a St. Bernard and go sit on a bridge in Amsterdam and make music. The only snag is that I shall be doing some colleague out of 4½*d*. a week—or will it be 9*d*.?

* * *

My erudite friend mentioned it in his differential diagnosis and then, as is his habit, passed swiftly on. "Asthma of the hair follicles." I had not heard of it before, but wishing to conceal my ignorance I hurried off to search the books. It was not mentioned in the usual textbooks or in the great encyclopædias of medicine. I could not find it in the general medical journals, and even the special journals with monolithic names, like *Brain*, *Blood*, and *Thorax*, which have always seemed as unapproachable and unassailable as Chomolhari and Lhotse, did not help. Desperate by now, I searched the back numbers of *Skin* and *Tooth and Nail*, but to no purpose. In the end I have had to draw on my imagination. In my mind's eye I see one of our great contemporary physicians deep in thought with his stethoscope swinging idly from his ears, its great chest piece, a mass of trumpets, taps, and drums, passing slowly to and fro across his patient's hairy chest. Suddenly he picks up a strange sound like a million minute wheezes fused together, or the murmur of a miniature breeze in the trees of a tiny Japanese garden such as we had on our mantlepiece at home in my youth. It is a staccato sound, like micro-machine-guns firing in that forest of hair, or the croaking of a thousand tiny bullfrogs—*Brek-ek-ek-kex-thorax-thorax.*

* * *

Henry's response to the breast-feeding concept was different from both the examples described in these columns. Henry, who is 7, had learnt with interest that his mother was taking orange-juice and the new baby would need it too. So later, when told how the newcomer was to be fed, he asked the obvious question: "Mummy, do you have milk on one side and orange-juice on the other?"

* * *

Inquiry from School.—Please could you tell me how a person's appendix kills him when it is enflamed? *PS.*—I have really written this letter for the sake of putting your letters on the envelope, but I would like to know.

Letters to the Editor

INCOMPATIBLE TRANSFUSIONS

SIR,—I regret that my acknowledgments to Dr. Maycock, Dr. Mourant, and Dr. Parkin in my article (April 12) have been interpreted by some as claiming their approval of my methods. My words made no such claim, and I can hardly expect their approval when I retain crude methods which may have been adequate in pre-rhesus days, but which will fail to detect some antibodies now well known. Now that the freer use of small-pool plasma and dextran has reduced the need for hasty cross-matching, I shall probably adopt their methods for urgent cases; but these methods had not been published in 1946, when I started this experiment.

My results show four things:

(1) That the simplest methods of blood-grouping give rise to few incompatibilities if used by highly experienced and conscientious workers.

(2) That incompatible transfusions are usually caused by gross blunders, and not by obscure antibodies detectable only by the most refined serological techniques.

(3) That most patients recover from an incompatible transfusion without special attention.

(4) That anuria is not a common sequel of incompatible transfusion.

Most workers still believe that incompatible transfusion is lethal, in spite of the observations of Wiener and Dahr mentioned in my article. Dahr's figures indicate a 20%, mine a 10%, mortality. I believe that for every incompatible transfusion that attracts attention by causing anuria or death, there are between 5 and 10 other incompatibilities which do not cause anuria, and are either unrecognised or forgotten when the time comes for discussion.

It therefore follows that, within the average hospital, time and money will be better spent on improving the transfusion organisation than on increasing the delicacy of the test for compatibility—provided that ABO and Rh homologous blood are selected and some form of direct matching attempted.

The consultant in charge of a hospital blood-bank must ensure that records of every bottle, every recipient, and every special donor are readily accessible. He must insist that his clinical colleagues provide adequate information about the recipient. His decisions on details of organisation or on technical methods may well vary from hospital to hospital, and will depend not only on the type and number of patients admitted, but also on the capacity, temperament, and character of his assistants and colleagues.

His problems are quite different from those of the regional transfusion officer, and he should not necessarily be expected slavishly to accept the regional officer's advice—though he should never refuse it without preparing a formal statement of his reasons and without careful self-examination.

Central Middlesex Hospital,
London, N.W.10.
GEORGE DISCOMBE.

GERMAN MEASLES IN THE ADULT

SIR,—I have been noticing for a month or more the frequency of cases of dizziness, aches and pains about the body, frontal headache, and feelings "as if the limbs are made of rubber," mostly without much rise in temperature. The pains did not seem to be rheumatic, for they were almost always accompanied or followed by bronchitis, and when severe by "pins and needles," numbness, and a sensation of cold in the limbs. Many of these patients presented with diffuse enlargement of their lymph-glands, and it was the glandular enlargement that linked this condition with german-measles, which is epidemic in the Manchester area. Once rubella was suspected, careful questioning usually elicited a history of a rash, often lasting only a few hours, and occasional "sweats" also.

This year's rubella is associated with more glandular enlargement than usual; and instead of having to feel for the typical "shotty" glands behind the ears and at the nape of the neck, the postauricular and other glands are often swollen enough on each side to be visible. The enlarged glands may appear a week before the rash, and sometimes persist for several weeks after it; in two cases the Paul-Bunnell test was negative.

I have seen two cases of painless enlargement of prepatellar bursæ, and one of the bursa on the elbow; these had all come up for no apparent reason in one day and lasted only two days; there is no evidence that they were connected with rubella.

One woman complained of "toothache" in her lower jaw, though her fillings seemed sound; and she also had a sore throat, felt at the *root of the neck*, with a choking sensation. The same throat symptoms, lasting for a couple of days, have been complained of by other patients.

The symptoms of this outbreak seem to be exceptionally variable. A central creamy coating of the tongue is the only constant finding.

Manchester, 16. S. SHUBSACHS.

*** See annotation and notification figures last week (pp. 1057 and 1073).—ED. L.

SYNERGY OF HEALTH AND EDUCATION

SIR,—As a schoolmaster I have seen the work of the School Health Service over a number of years and I was surprised to read in your leading article of May 10 that the main criticism of the service was directed against "routine" medical inspection. Possibly more of the work might be done by nurses (though we are always told nowadays that there is a great shortage of nurses) and possibly the work may become monotonous and be done perfunctorily at times, but without a regular inspection by a qualified doctor I can see no way in which defects could be discovered at an early stage, or minor emotional difficulties overcome before they have seriously affected a child's whole life.

The service may make heavy demands on valuable medical man-power, and no doubt its expense is kept under constant review; but there can surely be no doubt of the immense benefits which are directly due to the "routine inspection" or of the great saving in suffering as well as money that the service has achieved in the past fifty years.

HEADMASTER.

FLUORIDATION OF WATER-SUPPLIES

SIR,—In your issue of May 10, Colonel Mackenzie leads us to suppose that any outcry against the fluoridation of water-supplies would come from "a small and for the most part uninformed minority." But there are many knowledgeable people who oppose such a policy.

In the U.S.A., where "well-advised publicity . . . has enabled the public to give an informed opinion on policy," the authorities of Beverly Hills, Minneapolis, Saint Paul, and Lincoln have refused to install fluoridation plants. In Wisconsin three fluoridation plants have been removed in response to public demand. Moreover, Congress has reduced the estimates for the fluoridation scheme from $2,000,000 to $250,000. The U.S. select committee on chemicals in food and cosmetics has not yet reported on fluorine, but a member of the committee, who was originally in favour of fluoridation, reversed his opinion after the committee's hearing of the evidence.

The British public, Colonel Mackenzie declares, "is almost completely ignorant of, or quite indifferent to, the benefits that may come from fluoridation." But there are many who await with interest the report of the scientific team which is at present studying the subject in the U.S.A. No plans for fluoridation in this country should go forward until this report is published.

As the husky parts of wheat are said to be the main source of fluorine in the diet, is not calcium-fluophosphate better for our health than sodium fluoride? If doctors and dentists would only help to stop the adulteration, deprivation, and gassing of our food, then our teeth and bones would be as Nature intended.

Mass medication is immoral whatever the argument for any particular medicine may be; it is against the internationally accepted principles which govern medical experiments on human beings. It cannot be justified by quoting enforced additions to our food in the past. The freedom to choose or refuse—"the right to contract out"—is fundamental. If we are to be given fluorine we must also be given full information on easy household methods of removing it from drinking-water.

2, Stepney Green,
London, E.1.

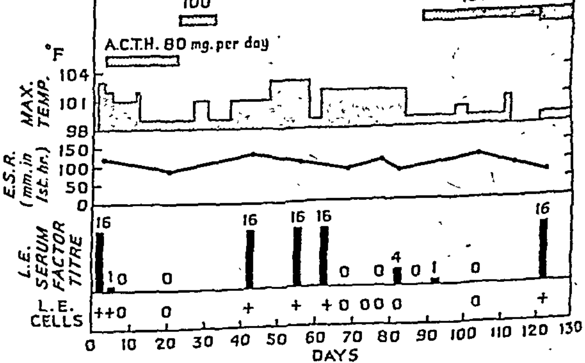
WINIFRED M. SYKES
Vice-chairman,
British Housewives' League.

QUANTITATIVE ASSAY OF L.E. CELLS

SIR,—The so-called lupus erythematosus (L.E.) cell, first described by Hargraves et al.[1] in 1948, and the serum factor producing it[2] are now recognised as characteristic features of this disease. During a lengthy study of several patients with disseminated lupus erythematosus, and especially in trying to assess their response to treatment with A.C.T.H. and cortisone, we have used a quantitative method of following the L.E. serum factor.

About 5 ml. of venous blood is withdrawn; 1 ml. of this is mixed with an anticoagulant, such as Wintrobe's mixture or heparin, while the rest is allowed to clot and the serum removed. The 1 ml. sample is then incubated at 37°C for thirty minutes and subsequently centrifuged in a Wintrobe tube at 2000–2500 r.p.m. for fifteen minutes. Smears made from the buffy coat mixed with a little of the supernatant plasma are stained by Leishman's method.

To demonstrate the L.E. serum factor, doubling dilutions, 0·5 ml. each in a 3 × $^1/_2$ in. tube, are made for a range from 1 : 1 to 1 : 128 and extended, if necessary, to the final titre. To each tube 0·5 ml. of washed cells is added from a healthy donor. (Cells from the same group-O rhesus-negative donor were used throughout this investigation. A control test, using this donor's own undiluted plasma and cells was commonly put up simultaneously, but at no time were L.E. cells observed therein.) The mixture of cells and serum is incubated at 37°C for thirty minutes, and then centrifuged and stained as for L.E. cells. All smears are examined for fifteen minutes under the microscope, covering the whole film and using the low-power ($^2/_3$ in.) objective and an 8x eyepiece. Suspicious cells are examined more closely with the oil-immersion objective ($^1/_{12}$ in.).



Findings in a 26-year-old woman with disseminated lupus erythematosus.

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[1] Hargraves, M., Richmond, H., Norton, R. *Proc. Mayo Clin.* 1948, 23, 25.

[2] Haserick, J. R., Bortz, D. W. *J. invest. Derm.* 1949, 13, 47.

In this investigation the L.E. cell phenomenon was said to present as soon as one such unequivocal cell had been und in any film. No attempt has been made to assess the mber of L.E. cells in a smear. For the serum factor, the ghest dilution of serum producing L.E. cells was recorded as e titre. The so-called "rosette" phenomenon, in which ucocytes are seen to surround a lump of amorphous matter nd which is often observed in cases of disseminated lupus, as not accepted as positive evidence.

Since the results have essentially been similar for all itients, the details are given for only one case (see figure). he level of serum factor, which never rose above a titre 1 : 16, could not be correlated with the activity of the lness. Though A.C.T.H. and cortisone acetate benefited ie clinical condition of the patients, these hormones id not apparently affect the titre of serum factor. xcept on one occasion, serum factor was never demonrated in the absence of L.E. cells by the direct method.

The patient for whom detailed data are given was under ie care of Dr. E. G. L. Bywaters.

Canadian Red Cross Memorial Hospital,
Taplow, Maidenhead.
G. LOEWI.

TREATMENT OF ROSACEA WITH MEPACRINE

SIR,—In his report on the treatment of lupus erythematosus with mepacrine, Page[1] postulated that the drug night act by decreasing the sensitivity of the skin to ght, and suggested, for this reason, that it might be of se in rosacea. A small, controlled series of patients rith cutaneous rosacea have been treated with mepacrine t Moorfields Hospital. The results are shown in the ccompanying table.

28 consecutive patients with cutaneous rosacea took part n the trial. All the patients except 4—2 in each group—also ad ocular rosacea. Alternate patients were given mepacrine, nd the remainder were treated with topical sulphur emulsion ; o other form of therapy was applied. The dose of mepacrine ras 300 mg. daily until pigmentation was noticed, and hereafter 100 mg. a day.

The 1 patient who showed improvement with mepacrine ubsequently relapsed and did not respond to a second course. other patient, not included in this series, took mepacrine or nine months and showed a 75% recovery, which she has ince maintained.

The percentage recovery in each of the two groups of 14 cases, assessed after an average of ten weeks' treatment n the group treated with mepacrine and of seven weeks in the group treated with topical sulphur emulsion, was as follows:

Percentage recovery	*Mepacrine* (*no.*)	*Sulphur emulsion* (*no.*)
100	0	0
75	1	11
50	0	2
25	0	1
0	13	0

This series suggests, therefore, that mepacrine is of little use in cutaneous rosacea. Since 1 patient did improve, however, after taking the drug for nine months, it might be worth giving it for a long period to patients who have failed to respond to all other forms of therapy.

London, W.1.
PETER BORRIE.

ISONICOTINIC ACID HYDRAZIDE AND STREPTOMYCIN RESISTANCE

SIR,—On Feb. 28, 1952, 12 stock guineapigs were inoculated subcutaneously with a suspension of *Mycobacterium tuberculosis* containing approximately 10 million organisms of the H37RV strain. On March 13, 6 of the guineapigs were started on a course of isonicotinic acid hydrazide prepared in this country by Antigen Laboratories Ltd. They were given 10 mg. per kg. body-weight daily in two divided doses for six days a week. This régime was followed for nine weeks after which 3 of the treated and 3 of the untreated animals were killed. Necropsy showed marked localisation of the disease in the treated animals.

Another 4 animals were inoculated with a streptomycin-resistant strain and 2 of these were given a similar course of isonicotinic acid hydrazide. Post-mortem examination revealed extensive disease in the controls, but the treated pair showed nothing beyond enlargement of the local lymph-node.

These results confirm the inhibitory effect of the drug on both normal and streptomycin-resistant strains. Experiments to determine the sensitivity of the recovered organisms to isonicotinic hydrazide are in progress.

K. F. W. HINSON
The London Chest Hospital.
Director of Pathology.

WHAT SHOULD THE NURSE BE TAUGHT?

SIR,—Miss Ottley (May 17) asks what alternatives to nursing duties are likely to be acceptable by young girls employed in hospitals so that they may earn the wages provided by the taxpayer. It may be of general interest to describe the scheme operating in my own group. It should be understood, however, that the scheme is experimental and it was not intended to publicise it until more experience had been gained.

Entrants are accepted between 15 and 17 years of age, although we are now tending to take candidates at 16 rather than 15 years. The total hours of attendance at hospital and school are 40, of which two whole days are spent at school by arrangement with the local education authority. The syllabus of school work is wide and includes English, arithmetic, general science, speech training, and various recreational activities (e.g., music and handicrafts). Three days, of 8 hours each, and one half-day (4 hours) are spent in hospital. A period of approximately three months is spent in some or all of the following departments carrying out the duties detailed:

Linen Room.—Sorting, checking, learning how to carry out various types of mending and marking, messages, learning the use and care of linen.

Occupational Therapy.—Preparation and care of materials, dusting, storing equipment, messages, simple office work.

X-ray Department.—Dusting and polishing furniture, cleaning sinks and washbasins, care of linen (sorting and mending), telephone messages, delivery of films and reports, helping in the dark-room.

Nurses' Home.—Issuing of linen and personal laundry, telephone messages, helping new staff to find their way about, location board.

Diet Kitchen.—General assistance with preparation of food, simple cooking, assisting with general cleanliness, messages, care and cleaning of equipment.

Offices.—Messages, simple office procedure (e.g., duplicating, filing, labelling, and simple cleaning).

It is impressed upon the heads of all departments in which these cadets are employed that in no circumstances are they to enter the wards or have contact with patients in the wards. We have found that heads of departments are very coöperative and quite willing to teach the rudiments of the work in each department to these cadets, and in return find their willing help very useful indeed. In my own office many routine jobs which the cadet carries out are arranged so that they may be done when she is not at school, and I am satisfied that the taxpayer is more than getting his money's worth from these girls.

The cadets receive an allowance of 33*s.* a week for the first year of the course and 37*s.* a week after the first year. In this industrial area this allowance is extremely small, and it is not uncommon to find mills offering girls leaving school £3 15*s.* a week to learn cotton trades.

At the present time there are 24 cadets in training. All have joined the British Red Cross Society; 17 have passed their home-nursing examination, and all are now taking the first-aid course. These classes are voluntary and are taken in the evening. So far we have lost 2 cadets, but as I have pointed out, it is too early to assess the results of this scheme as the first batch will not enter their general training until later this year.

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[1] Page, F. *Lancet*, 1951, ii, 755.

I believe that such an experiment as this is worth while if carefully controlled, and it provides the following advantages:

1. It enables girls who have not had the advantages of a secondary-school education to continue their education, even though part-time, before taking up their general training.
2. Girls who leave school at 15 years with a desire to nurse are kept interested in hospital work until they are ready to start their training.
3. The prospective student nurse is given an insight into the workings of the many departments which go to make up a modern hospital, of which otherwise she would have little or no knowledge.
4. Assistance is given to departments, often hard-pressed, which in these days of financial stringency could not afford to employ an additional adult.
5. I believe, although this has yet to be proved, that wastage figures from this selected group will be smaller than a similar unselected group when training proper starts.

There are a number of essential features which must be incorporated if success is to be achieved. Among these are:

1. A spirit of coöperation and enthusiasm on the part of the hospital authority on the one hand and the local education authority on the other.
2. Recognition by all concerned that on no account must these young girls be allowed to do nursing duties.
3. Willingness on the part of departmental heads to teach these girls and to ensure that they are kept fully occupied during their spell of duty.
4. The same high standard of conduct must be demanded from cadets as from nursing staff generally.
5. Money allowances must be small enough to ensure that girls are not attracted by this in competition with industry or commerce.

S. Hodkinson
Secretary,
Rochdale and District Hospital
Management Committee.

Rochdale.

EARLY DUMPING SYNDROME AFTER GASTRECTOMY

Sir,—We have been interested in your correspondents' remarks on our paper of March 29.

We were aware of the method, suggested by Dr. Pulvertaft (April 12) and Mr. Downie and Dr. Hilliard (April 19), of radiological examination of the upper gastro-intestinal tract after ingestion of a normal meal impregnated with barium; for we were familiar with its use by Dr. E. Perman and his associates in Stockholm. But we preferred to employ the standard barium meal for two reasons: (1) because we already had an established base-line of normality, gained during innumerable routine barium-series examinations, from which to measure variations in alimentary mechanics after gastric resection; and (2) because the adoption of this method enabled us to fit our studies more conveniently into the routine of a busy X-ray department.

Mr. Moroney (April 12) rejects our strictures on his method of colon replacement after gastrectomy with perhaps some of the indignation of a fond parent defending the virtues of a cherished child. As we were careful to point out, our cases submitted to this technique were too few and too recent to permit of any accurate estimate of its success, relative to other forms of gastrectomy, in minimising the incidence and severity of dumping. But we could not fail to be impressed by the fact that, contrary to the experience of Mr. Moroney, several of our patients had quite severe postprandial discomfort, and to reach the conclusion that colon replacement was no infallible preventive of dumping. Mr. Moroney would dismiss these symptoms as due to the small-stomach syndrome rather than to true dumping; but we are not sure how these two allegedly different syndromes can be distinguished from each other. The duodenal leaks after colon replacement in 2 of our cases (1 of them fatal) might admittedly have occurred after more orthodox forms of gastrectomy; but we cannot quite banish f our minds the suspicion that these may in part have attributable to the technique employed.

St. Mary's Hospital,
London.

J. C. Goligher
T. Richard Riley.

ROYAL COMMISSION ON MENTAL HOSPITALS

Sir,—Surely we should have a Royal Commission o the mental-hospital system, to review, independentl and without bias, the whole position. It is at least quarter of a century overdue.

London, N.W.4.

A. L. Rowson.

BILIRUBINÆMIA AS A DEFENSIVE FACTOR

Sir,—I have for some years been collecting evidenc to show that the constituents of bile may play a important part in resistance to infection, and I shoul like to draw your readers' attention to observations an experiments which support this theory.[1–6]

Some pathogenic organisms are partially or wholl soluble in bile—e.g., pneumococci, spirilla, spirochæte and certain viruses. The finding of Lefèvre[7] confirms m experiments with pure bilirubin which show that it destructive action on these organisms is several time greater than that of bile salts. Other organisms ar insoluble in bile and may even thrive in it. This grou includes streptococci, staphylococci, gonococci, *Myco bacterium tuberculosis*, *Salmonella typhi*, *Vibrio cholera* and certain viruses.

Parlange[8] has produced spectacular improvement i trachoma by applying bile to the infected lids. His resul could be explained by the fact that the virus of trachoma bile-soluble.

Clinical and biochemical evidence[4] has suggested t me a classification of infections into those which ten to produce jaundice and those which do not. Th important point is that infections caused by bile-solubl organisms are associated with a rise in the plasma bilirubin level, whereas in those due to bile-resistan organisms the plasma bilirubin remains normal o decreases. The degree of hyperbilirubinæmia in th first type depends on the sensitivity of the pathoge to the lytic action of bilirubin, on the nature of th infection, and on the output of bilirubin from the reticulo-endothelial system. (In either type of infectio an *obstructive* jaundice may complicate the illness and this event must be distinguished from the direc response to a bile-soluble organism.)

The bilirubin content of normal human plasma repr [illegible] balance between output fro the [illegible] ystem and elimination by th liver. In my view this constant level provides a defenc against both kinds of infection. On the one hand, bilirubin is an enzyme activator which makes bacteriolysis of the bile-soluble organism more effective—a bacteriolytic action. On the other hand, bilirubin exerts a chemotactic effect on those organisms which are insoluble in bile, and, by attracting them to its molecule, carries them away from the tissues and eliminates them through the hepatic filter—a bacteriostatic action.

Bile salts may also take part in the defence mechanism. I think there is sufficient evidence to suggest that bile salts are not excreted only into the biliary system but also pass directly into the blood-stream. Whether thi is so or not, I have found that the level of bile salts in the blood shows a rise and fall comparable to that of bilirubin, according to the nature of the infecting organism. The main physiological action of bile salts is

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1. Najib-Farah. *Lancet*, 1937, i, 505.
2. Najib-Farah. *J. trop. Med. Hyg.* 1938, 41, 40.
3. Najib-Farah. *Acta rheum., Amst.* 1939, 11, 2.
4. Najib-Farah. *J. Egypt. med. Ass.* 1948, 31, 522.
5. Najib-Farah. *Sem. Hôp. Paris*, 1950, 26, 3197.
6. Najib-Farah. *Rheumatism*, 1952, 8, 1.
7. Lefèvre, J. Manuel Critique de Biologie. Paris, 1938; p. 639.
8. Parlange, J. A. *Maroc méd.* 1949, 28, 724.

assist digestion by certain lipases and by trypsin; ey do this by emulsifying fats. These and other enzymes e present in the blood [9] and it may be that bile salts able them to digest bile-soluble organisms in a similar ay. According to Barron [10] bilirubin is normally in an dsorbed state, attached to one of the constituents of lasma, probably globulin. In this form it is not excreted y the kidney and gives only an indirect van den Bergh eaction. The bile salts, by lowering surface tension, ay liberate the bilirubin, which in the free form gives a irect van den Bergh reaction. Moreover, free bilirubin an diffuse more readily into the tissues, producing linical jaundice. It is thus able to pursue the bile-oluble organism even after it has left the blood-stream.

Warm-blooded animals, including man, can be divided into wo groups—those in which bilirubin is normally present in he blood and those in which it is not.[4] It is interesting to note that the first group includes man and other animals whose heads are generally well above the ground, whereas animals with no bilirubin in their blood are those whose faces are usually close to the ground. Soil-borne infections are often caused by bile-resistant organisms, against which bilirubin would give little protection, but airborne infections, such as pneumococcal pneumonia, are predominantly due to bile-soluble organisms which are less likely to flourish when there is bilirubin in the blood.

Cholesterol exerts a control over cell permeability and membrane equilibrium, and may therefore influence the rate at which toxins diffuse into the body cells. The blood-cholesterol level falls during a pyrexial illness, suggesting that cell permeability is diminished and toxic damage minimised.

My observations may help in the further elucidation of rheumatoid arthritis, the symptoms of which are relieved during an attack of jaundice whatever the cause. I have suggested that an infection by a bile-soluble organism has the same effect on the disease, because it gives rise to an increase in plasma-bilirubin. The action of cortisone and A.C.T.H. in rheumatoid arthritis is not curative, and there must be other factors as yet undetermined. Perhaps bilirubin, bile salts, and cholesterol may fit somewhere into the complete picture.

Alexandria, Egypt. NAJIB-FARAH.

ESTIMATION OF DINITRO-ORTHO-CRESOL IN BLOOD

SIR,—When Parker's[11] method of estimating dinitro-*ortho*-cresol (D.N.O.C.) was applied to a 1 in 10 dilution of blood, it was found that the colour of the ketone extract obtained was very faint for all blood-levels of D.N.O.C. likely to be encountered. Some modifications of the method introduced by Harvey[12] were felt to be of limited application in a region where a considerable number of specimens is received by post at the central laboratory.

After trial of various proportions of ketone, blood, and water the following method of estimation was found to yield a ketone extract sufficient in volume and colour intensity to be read in the Spekker photo-electric absorptiometer, using standard 1 cm. cells and Ilford 601 filters:

> To 1 ml. water in a ground-glass stoppered test-tube are added 1 ml. oxalated blood, 5 ml. ethyl methyl ketone, and excess salt mixture.[1] After shaking, a slip of paper is inserted between the glass stopper and the rim of the test-tube, to prevent impaction, and the emulsion is centrifuged for 15 minutes at 2500 revolutions per minute. The optical density of the ketone extract is read, and the blood-D.N.O.C. found by multiplying by 5 the figure obtained by referring the Spekker reading to a standard curve prepared for the estimation of D.N.O.C. in urine.[1]

Good recovery values from blood were obtained by this method, while no trouble was experienced from emulsification of blood and ketone; and no special apparatus is required.

Biochemical Laboratory,
Royal Northern Infirmary,
Inverness.

JAMES BRUCE
ROBERT MACKAY.

TEACHING EVOLUTION IN THE SCHOOLS

SIR,—Dr. Spanner's letter last week is a welcome sequel to your annotation of April 26 on Prof. Julian Huxley's missionary manifesto. Evolution as a universal principle is actually taught widely in our schools, and is taught badly in two notable respects: (*a*) the teachers' biological background is commonly inadequate, and (*b*) the theory is, by unwarranted and undisclosed assumptions, elaborated into a religion.

Biologically, the popular teaching of evolution is still in the period of naïve 19th-century materialism, unhumbled by the newer knowledge of genetics, biochemistry, and atomic physics. The approach is such as to shrivel the sense of wonder in young minds, with the facile assurance that "evolution brought this about," whether *this* be some interlocked sequency of enzyme and co-enzyme action, or one of the more amazingly precise instances of adaptation and design. I agree that the time is ripe for renewed study of the sciences, freed from bondage to the prejudice that at any cost an atheistic explanation must be found. Much splendid energy has been sidetracked by this bias in the last ninety years. The urge has been too one-sided—to explain away the beauties of the universe, even presuming upon the territory of inanimate chemistry and astronomy.

More insidious, though, is the fashion for expanding the realm of "evolution" into a philosophy of the universe and of life and society, a religion (without revelation), a self-styled "scientific" humanism.

While respecting the personal convictions of all men of science, the public are entitled to two major safeguards in the education of our children. First, the line must be distinctly drawn between ascertained fact and theory, and between scientific hypothesis and philosophical opinion or conviction, where these distinctions involve separate planes of thought. School-children and many undergraduates are not equipped to offer critical resistance to confused indoctrination. Secondly, education must not take for granted that science alone can afford the whole answer, or even the chief answer, to the ultimate problems of the origin and meaning of our life and destiny.

Doncaster. CEDRIC C. HARVEY.

SIR,—I should like to express my strong support of Dr. Spanner's point of view. The evolutionary hypothesis is interesting as a possible reconstruction of the natural history of the world and also as a commentary upon the prevailing ideas and outlook of the time when it was proposed. As value concepts are foreign to its terms of reference, it provides no basis for ethics; and it should not be taught until the developing mind has some ability from experience and from training in reasoning, as well as a sufficient store of factual information, to appreciate it at its true worth. Thus the stratagems of that school of thought which, because of family tradition or political predilection, has a vested interest in the promulgation of neo-Darwinism, ought to be resisted.

The young should early be taught what is the proper sphere of natural science. As it deals solely with the "how" of things, its concern is with contingent events, the results of causes themselves contingent and expanding into a universe where finality (like the theoretical number of one's ancestors) can never be reached. Dr. Spanner will no doubt remember the Third Proof of St. Thomas

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9. Oelgoetz, A. W., Oelgoetz, P. A., Wittekind, J. *Amer. J. digest. Dis.* 1936, 3, 549.
10. Barron, E. S. G. *Medicine, Baltimore*, 1931, 10, 77.
11. Parker, V. H. *Analyst*, 1949, 74, 646.
12. Harvey, D. G. *Lancet*, 1952, i, 796.

Aquinas, which argues from contingent to necessary being. The application of this is particularly apt at the present time, when science is becoming increasingly confused within the jungle of discovered facts where unification on the natural plane is ever more impossible. According to this reasoning, the creational act of God is to be considered not only as ultimate but as immediate, since by the continuous operation of the divine Will everything is held in existence and every contingent act permitted. Thus the work of creation underlies every mutation of the genes (if such in fact occur), though when described scientifically they could only appear to be chance effects. So too, directly and immediately, is the human soul created at the moment of conception.

Darlington.

JOSEPH V. WALKER
Medical Officer of Health.

RELAXATION IN LABOUR

SIR,—While agreeing with Dr. Newbold (May 24) on the value of hypnotism in childbirth, I should like to point out that the relaxation produced is of great use in a far larger range of medical conditions than is generally realised. Ultimately, no matter what technique is used, success in hypnotherapy depends upon skilful, scientific suggestion (not mere removal of symptoms); and for the purpose of providing postgraduate training in the subject, the London School of Medical Hypnotism has been established under the auspices of the British Society of Medical Hypnotists.

London, W.1. **S. J. VAN PELT.**

FUNCTIONAL DISORDERS AFTER GASTRECTOMY

SIR,—Dr. Haler and Dr. Blond, pleading last week "for reconsideration of the ætiology of gastroduodenal ulceration," made two statements so inaccurate that I feel they should not go unchallenged.

They state: "a surgeon removes the bulk of a healthy stomach—in order to treat an ulcer in the duodenum, which is left intact with its ulcer." The operation for a duodenal ulcer is a [illegible]. A major portion of the stomach [illegible] duodenum containing the ulcer are removed. Nor is the stomach invariably "healthy," for it may show very severe hypertrophic gastritis with gross bulging of the mucous membrane, such as is not seen in the normal stomach.

Maidstone. **B. E. CRAWFORD STANLEY.**

CARDIAC ARREST

SIR,—The following case may be of interest, for it illustrates how, when the heart has stopped beating for long periods, the injection of adrenaline into the heart-muscle may virtually bring back life to the dead—even at an advanced age.

The patient, aged 82, an ex-varnish-maker of sturdy build, collapsed suddenly in the hospital gardens. When he reached the ward he was pulseless with Cheyne-Stokes breathing. He was given oxygen and nikethamide, which restored his pulse for about 3 minutes, only to vanish again. He was given artificial respiration, and after a time his heart again gave a few feeble beats. It then stopped apparently for good. Over the next 15 minutes the only signs of life were two long-drawn-out, rattling sighs characteristic of death. After this he was apparently lifeless; his eyes had glazed and become soft to the touch, and his face had the yellow, waxy appearance of death. His body had cooled despite hot-water bottles.

0·5 ml. of adrenaline hydrochloride was then injected into the heart-muscle, with surprising results. After about 30 seconds the heart began beating again, at first with irregular rhythm and inconsistent volume, but improving rapidly. After 3 minutes the patient took a spontaneous breath. In 5 minutes the corneal reflex had returned, and in 10 minutes he moved an arm. The patient was muttering after 20 minutes, and after an hour he had recovered consciousness. It is interesting to note that, for the 35 minutes up to the tim was given the injection of adrenaline, his heart had not active for more than 5 minutes in all.

There have been no after-effects and the patient now as well physically as he has ever been. Curiousl enough, as part of his pre-existing psychotic illness, t old man expresses the strange delusion that his bo will not carry out its natural functions.

I am indebted to Dr. R. Macdonald, the physician-sup intendent, for permission to publish this case.

Banstead Hospital,
Sutton, Surrey.

C. G. F. SMARTT.

VARIATION OF EOSINOPHIL-COUNTS

SIR,—In your issue of May 17 Dr. M. J. H. Smi questions the validity of a conclusion based on eosinoph counts made on blood taken in the morning, as "It h recently been emphasised that the morning is an unsu able time for measuring induced falls in eosinophi because 'spontaneous' decreases may be as large as 50 (Swanson et al. [*Lancet*, 1952, i, 129])."

We have in a large series of observations[1] come to t conclusion that counts taken at 10 A.M. and 2 P. under standard conditions of observation (physical a mental rest) very rarely show spontaneous decreas of any magnitude, and that they are a reliable a sensitive index of induced adrenocortical stimulatio The importance of standardising the conditions und which these observations are made has not been suffi ently stressed, and it would be regrettable if the conclusi that morning counts are unreliable were genera accepted.

Clinical Research Unit,
Three Counties Hospital,
Arlesey, Beds.

F. MACKENZIE SHATTOCK.

COÖPERATION IN RESEARCH ON HEART-DISEASE

SIR,—Special inquiries were sent recently from t General Register Office to all doctors in London and t Home Counties who certified the death of a patie aged 40 or over, from cardiovascular, renal, or respirato disease, during the first fortnight of March, 1952. Th doctors were asked to provide additional informatio about their late patients in order to assist the Soci Medicine Research Unit of the Medical Research Coun in its studies of the prevalence of heart-disease a hypertension in the population.

The response has been very gratifying, and we wish to tha the large numbers of practitioners who coöperated in t inquiry; there is no doubt that valuable information h been obtained.

However, the value of an inquiry of this type is mu enhanced if something like a 100% response can be obtain We appeal therefore to any practitioner who received questionnaire and has not yet returned it to do so now. particular it would be helpful if doctors who have not return the questionnaire because they no longer have access to t patient's records—for example, at the hospital where died—would send the form to the hospital (to the *medi* registrar, for instance) for completion and return. If this not practicable we should be grateful if the form were return uncompleted to the first of the undersigned, with a note abo the reason, at Kenworthy's Hydro, Southport. As is emphasis in the covering letter to the questionnaire, the method adop for the inquiry fully preserves the confidential nature of t additional medical information being provided.

W. P. D. LOGAN
Chief Medical Statistician
General Register Office.

London, W.C.2.

J. N. MORRIS
Director,
Social Medicine Research U
Medical Research Council

Central Middlesex Hospital,
London, N.W.10.

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[1] Shattock, F. M., Micklem, L. P. *J. ment. Sci.* 1952, 98, 28

Medicine and the Law

Not Negligent?

Prof. Ian Aird's letter in the *Times* of May 23 invited attention to the regrettable consequences of the present procedure under which a medical practitioner or a hospital (or indeed both together) may be sued by a patient for damages for alleged negligence. How enviable is the immunity of another of the learned professions! If a barrister discharges his duty honestly, his clients cannot sue him for negligence or for any want of skill, discretion, or diligence in the course of his professional actions. Nay more, if the barrister accepts a brief and a fee with it, the client cannot even recover the fee if the barrister omits to attend the trial.

The word "negligence," Professor Aird contends, is much to blame for the liabilities and the legal claims which distract the surgeon and physician. It connotes something so culpable, so suggestive even of criminality, that the medical defendant must fight the allegation. If only some milder synonym could be substituted, he argues, much anxious and expensive litigation could be averted by friendly settlement at an early stage; the uncomfortable atmosphere of suspicion and disputed responsibility could be cleared away. Three advantages would follow. The normally happy relations between the governing body of a hospital and its consultants would not be poisoned; the medical records of the patient, set down objectively by the practitioner in the course of diagnosis and treatment, would not become a quarry wherein skilful and probably hostile explorers would later dig for incriminating admissions; and consultants would feel less hesitation and embarrassment in offering expert evidence for what Professor Aird describes as "a plaintiff, however deserving, or a hospital governing body, however harassed."

What euphemism can be substituted for "negligence"? Default, omission, carelessness, or inattention—none of these seems the perfect alternative. Eminent civil servants, when forced to admit a mistake, have been known to conciliate criticism by conceding that the erroneous action must have been *per incuriam*. To turn from Latin to Greek, paraleipsis (if introduced into popular currency) might have the same disarming effect of mystery and of flattery to the hearer's intelligence. Non-feasance, misfeasance, and malfeasance are, in another context, accepted legal terms, each with its own fine shade of meaning. But how do we persuade the judges to alter their vocabulary? An Act of Parliament would be needed to eliminate the tort of negligence from the common law. Is the legislature likely to intervene for the special benefit of the medical profession?

Explosion in Operating-theatre

On April 28, at about 10 A.M., an explosion took place in no. 2 operating-theatre of the Middlesex Hospital. The patient, who had been prepared for a hysterectomy, was in the Trendelenburg position on the operating-table with the drapes in place, but the operation had not begun. Closed-circuit cyclopropane and oxygen was being administered.

Up to the time of the explosion the anæsthetic had been uneventful. Induction was with thiopentone sodium 0·6 g. and maintenance with cyclopropane and oxygen using a circle absorber. The patient had been on closed circuit for 20 minutes when the explosion occurred; no drapes or mackintoshes were being moved, and there was no diathermy or other accessory electrical apparatus in the theatre. All earthing arrangements appeared to be satisfactory.

It seems most likely that the static spark was generated by the movement of the breathing bag during controlled respiration. Exhaustive investigations have been carried out, and will be published later.

At the inquest, the coroner, Dr. W. Bentley Purchase, said that the patient had died as a result of a sudden increase of pressure in the anæsthetic apparatus under which she was already anæsthetised. Her chest and tissues round the lungs had been damaged. There were two theories for the cause of the explosion, both of which invoke the possibility of a spark due to static electricity and also imply that there was an explosive mixture in the apparatus. Although the explosion occurred in that part of the apparatus which was most remote from the patient, the pressure was transmitted to cause internal damage. He was not prepared to give an opinion as to whether the spark was external or internal. Clearly, the leakage valve was quite normal and had its proper use on the apparatus. It was difficult to see how this sort of case could be prevented. The Middlesex Hospital (and Dr. A. J. H. Hewer in particular) had been extremely coöperative and had rendered every possible assistance to those who had been inquiring into the cause of the explosion.

Parliament

National Health Service Bill

In the House of Lords on May 20 the National Health Service Bill passed through the report stage and was read the third time. Lord Woolton gave an assurance that charges would only be made for appliances which were prescribed on or after the operative date. It would not be necessary to amend the Bill as this could be implemented by regulations.

The Bill received the Royal Assent on May 22.

Cremation Bill

In the House of Commons on May 23 the Cremation Bill, which embodies the recommendations of a Home Office Interdepartmental Committee appointed in 1947, was given an unopposed third reading.

QUESTION TIME

Hospital Administration

Mr. John Morrison asked the Minister of Health the number of persons whose full-time services were required for each inpatient in the hospitals of England and Wales.—Mr. Iain Macleod replied: It is estimated that the staff employed in 1950—many of whom provided services for outpatients as well as inpatients—were equivalent to 0·872 persons per occupied bed.

X-ray Examination of Army Entrants

In answer to a question Mr. Anthony Head, Secretary of State for War, said that at present nearly 70% of Army entrants got an X-ray examination, and the Minister of Labour was working towards 100% examination. Meanwhile, it was the policy to examine all new entrants, and this was being done in the vast majority of cases.

Dangers of Infections from Bone-meal

Mr. Gerald Williams asked the Minister of Agriculture what evidence he had as to the possibility that bone-meal and flour imported into this country could carry infection; and what regulations had been made concerning importation. —Sir Thomas Dugdale replied: Samples of imported bone-meal and flour have been analysed in the past and some have been found to contain anthrax, but there is no evidence that these products have been responsible for the introduction of other diseases. Bone-meal and flour are covered by the Importation of Carcases (Prohibition) Order, which regulates their importation from certain European countries, but their importation is allowed under licence.

Closed Shop Dispute

During a discussion at question time in the House of Commons on the threatened breakdown in public services in Durham, and possible preventive action on the part of the Government, Miss Irene Ward asked the Prime Minister if he could give the House any information about the health services and what line was to be pursued in that respect.—Mr. WINSTON CHURCHILL replied that there were various powers possessed in different degrees by the Ministries who might be concerned, but the Minister of Education had most clear and definite powers and used them.

Private Beds in London Hospitals

Replying to a question Mr. MACLEOD, Minister of Health, said that the number of pay beds set aside under section 5 of the National Health Service Act, 1946, in general (including teaching) hospitals within the Metropolitan police district was:

Regional hospital board area	*Pay beds*
North-West Metropolitan	590
North-East Metropolitan	144
South-East Metropolitan	287
South-West Metropolitan	341

Public Health

Old Age in Northern Ireland

IN China the old are privileged, in the United States the young. Neither arrangement seems entirely satisfactory; so perhaps we are fortunate to be living in a country where nobody much is privileged, nowadays. However, some are less privileged than others, and the old are probably the least privileged of all. Their necessities are much the same in Northern Ireland as they are here.

In their report[1] to the Northern Ireland Hospitals Authority, Dr. G. F. Adams and Mr. E. A. Cheeseman, PH.D., put the population of people aged 60 and over at 180,000, or 13% of the total population. In the coming decade they expect that both the numbers and the proportion will rise.

Of their survey sample of 759 old people they classify 54 as helpless, and estimate that this figure represents 12,700 old people in like case in the general population; and only about 2800 of these are likely to be able to be kept at home. Some 5600 of these helpless old people urgently need some home help, with or without medical or nursing care, and nearly the same number need it slightly less urgently. Outside Belfast, nearly a third of the old people living at home have no water-supply laid on, and have to carry their water, or have it carried, for longer or shorter distances. At the time of the survey 1625 old people were in general hospitals, occupying more than a third of the available hospital beds —maternity and children's beds excluded. In the mental hospitals there were 1716 old people. Adams and Cheeseman consider that 1379 of the patients in general and mental hospitals were fit for care in some other form of long-stay accommodation.

Probably more than 95% of the old people in Northern Ireland live in their own homes; and there are probably not more than 2000 beds available in voluntary or local-authority homes for old people needing residential care other than that given in hospitals. But then old people, there as elsewhere, dislike being taken from their familiar surroundings, and very few of the 7–9% who lived alone were discontented with their lot. Adams and Cheeseman suggest that, there as here, it is time that statutory welfare, health, and hospital services combined with voluntary services to provide the domestic, nursing, and medical care needed to maintain old people in their homes. The bodies concerned are the National Assistance Board, the welfare authorities, the General Health Services Board, the Hospitals Authority, the local health authorities, and a number of charitable organisations whose work is coördinated with that of the statutory agencies by the Northern Ireland Council of Social Service and the Belfast Council of Social Welfare. They recommend that a regional geriatric hospital service should be developed on the lines suggested by the British Medical Association in 1947. At present there are a 250-bed geriatric unit in Belfast and a 90-bed unit in Ballymena. Adams and Cheeseman suggest that four additional units, of 50–100 beds each, should be established at Limavady, Omagh, Lurgan, and Newtownards. Extra long-stay beds could be provided in Belfast, they think, in the old county hospital at Lisburn; and each of the new geriatric units would have its quota of long-stay beds associated with it. They also believe that the care of irremediable and homeless patients should be shared among all hospitals, including the acute hospitals, so that each carries a proportion of beds for these patients, either within the hospital or in annexes outside. Annexes could thus be kept small. One or two experimental annexes of the kind, for bedfast cases, should be established as soon as possible, attached to existing geriatric units. Annexes for frail ambulants are also needed urgently; and domestic help, more small dwellings for the old in new housing estates, more small residential homes, and convalescent homes are required for the elderly.

Their first and most important recommendation, however, is that *a geriatric advisory, or joint liaison, committee*, should be set up, on which all statutory bodies responsible for the medical and social care of old people are represented. This would join forces with voluntary bodies in the same field. The Northern Ireland Hospitals Authority, which sponsored the survey, has permissive power under the Health Services Act to form such a committee.

1951 in Eire

According to a provisional report,[1] the birth-rate in Eire last year was 21·2 per 1000 population. The death-rate was 14·3 per 1000 population; and the death-rate from all forms of tuberculosis was 0·7 per 1000 population. The maternal-mortality rate was 1·2 per 1000 births; and the infant-mortality rate, 45 per 1000 live births.

Obituary

JOHN WHARTON

M.A., M.D. Camb.

Dr. John Wharton, consulting ophthalmic surgeon to the Royal Infirmary, Manchester, died on May 5, at the age of 75.

His academic career was distinguished, for after leaving school he was elected a foundation scholar and a Hare's exhibitioner of St. John's College, Cambridge, where he graduated B.A. with first-class honours in 1898. After leaving Cambridge, he entered Owens College, Manchester, as a medical student, and he took the Cambridge degrees of B.CHIR. in 1902 and M.B. in 1903. After qualifying he became house-surgeon to the late Sir William Thorburn at the old Manchester Royal Infirmary. This was an honour, for Thorburn always picked the cream of the newly qualified.

About this time Wharton's thoughts turned to ophthalmology, and he obtained the post of junior house-surgeon at the Manchester Royal Eye Hospital, later becoming senior house-surgeon. In 1907 he proceeded to the higher degrees of M.A. and M.D. and the following year he attained his early ambition and was elected honorary assistant surgeon to the hospital. In 1910 he became full surgeon, a post he held until his retirement at the age of 65, when he was elected honorary consulting surgeon and a vice-president of the hospital. In 1923, Wharton was elected honorary ophthalmic surgeon to the Manchester Royal Infirmary, where he was responsible for the clinical training of medical students. He also became a clinical lecturer in ophthalmology in the University of Manchester.

Although not a prolific writer he wrote and published in 1918 a fine monograph on ophthalmia neonatorum. At that time this disease was a major scourge, and his work helped towards the establishment of a separate unit at the Royal Eye Hospital with its own laundry, where segregation of mother and child in single rooms was possible.

T. M. B. writes: "John Wharton had great strength of mind. His reasoning was calm and logical, and when he had reached a decision, either on a point of proessional conduct, or about the diagnosis of an obscure linical case, the matter was finished. He had thought t all out, and that was that. This habit gave him high-tanding with his colleagues when a final opinion was equired, for he was essentially a yes or no man when aced with a dilemma. His operative skill was excellent. He knew what he had to do and was a master when onfronted with difficulties. He once told me that he vas left-handed, but preferred to use the right. This imanualism materially helped him. Although somewhat eserved in manner, when he unbent he was a delightful ompanion. He concealed a kind heart and was a source f comfort and strength to many who sought advice rom J. W."

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[1] Old People in Northern Ireland. Belfast: Northern Ireland Hospitals Authority, 1951. Pp. 90, and appendices.

[1] Quarterly Return of the marriages, births, and deaths registered during [illegible] quarter, 1951, and yearly summary, 1951. Dublin [illegible] Office, 3–4, College Street.

Dr. WILLIAM BROWN

Sir Godfrey Thomson, D.SC., writes: "The news of Dr. William Brown's death was unexpected, for when I wrote to him on April 25 he was contemplating a return to the mathematical arena in which he had been an early ombatant on mental measurement, but from which his medical interests had taken him for many years. His 1911 monograph on the *Essentials of Mental Measurement* meant a great deal to me. It was brought to me one day that summer by Charles Myers, and led to my own activities in that field and to my undertaking its expansion, in the 1921 edition, under our joint names. A phrase in one of his last letters to me shows, I think, his attitude to life. 'My aim in life,' he wrote, 'is reconciliation, and I want to look forward, not back.' That attitude explains many of his later writings, especially his views on war and international politics."

Diary of the Week

JUNE 1 TO 7

Tuesday, 3rd

UNIVERSITY OF LONDON
5.30 P.M. (London School of Hygiene, Keppel Street, W.C.1.) Dr. C. M. MacLeod (New York): Transformation Reactions in Pneumococci. (Last of three lectures.)
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School, W.2
5 P.M. Dr. W. H. Bradley: Diphtheria—Beware! (Almroth Wright lecture.)
INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Street, W.C.2
5.30 P.M. Mr. A. K. Monro: Blood-vessels of the Lower Limbs.
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
5 P.M. Dr. S. Obrador Alcalde (Madrid): Surgical Treatment of Epileptic Patients.
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P.M. (Hammersmith Hospital, Ducane Road, W.12.) Mr. Keith Vartan: Breech Presentation.

Wednesday, 4th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
11.45 A.M. Medical clinical-pathology conference.
ROYAL EYE HOSPITAL, St. George's Circus, S.E.1
5.30 P.M. Mr. J. F. P. Deller: The Eye as an Optical System.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Medical Mycology—Microsporum and Epidermophyton Infections.
MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (Royal College of Surgeons, 18, Nicolson Street.) Mr. David Band, Dr. William A. Murray: Tuberculosis of the Kidney.

Thursday, 5th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
3.45 P.M. Mr. E. W. Grahame: Argentaffinomata of the Alimentary Canal. (Erasmus Wilson demonstration.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. Stephen Gold: Cutaneous Allergy.
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Section of United Services.* Brigadier A. Sachs: Prevention of Tetanus.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W.1
5 P.M. Sir Paul Mallinson: Psychiatry lecture-demonstration.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. H. Haber: Diagnosis by Biopsy and Cytology.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Prof. D. V. Davies: Synovial Joint.

Friday, 6th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
11.15 A.M. Surgical clinical-pathology conference.
2 P.M. Mr. Harold Edwards: Crohn's Disease.
4 P.M. Dr. Gold: Cutaneous Allergy.
ROYAL EYE HOSPITAL
4.30 P.M. Mr. A. J. Cameron: Surgery of Lacrimal Sac and Ducts.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Brian Russell: Reticuloses.

Births, Marriages, and Deaths

BIRTHS

BROCKINGTON.—On May 19, at the Fielding Johnson Hospital, Leicester, to Joyce (née Furze), wife of Professor Colin Fraser Brockington—a son.

LYLE.—On May 20, at the London Clinic, to Jane, wife of Mr. T. Keith Lyle, C.B.E., F.R.C.S.—a daughter.

MEIKLEJOHN.—On May 18, at Dundee, to Audrey Jean (née Ashforth), wife of Dr. William Meiklejohn, 334, Blackness Road, Dundee—a daughter.

MARRIAGES

BARTLETT—RITCHIE.—On May 17, at Ash, Surrey, Calum I. S. Bartlett, M.B., to Alice Marks Ritchie.

DEATHS

ADAMS.—On May 19, at West Ealing, Percy Edward Adams, M.D. Lond.

IBBOTSON.—On May 20, William Ibbotson, F.R.C.S.E., late of 78, Harley Street, London, aged 74.

PENMAN.—On May 11, at Birkdale, Southport, John Penman, M.D. Glasg.

Appointments

ALMOND, H. G. A., M.CH. ORTH. Lpool, F.R.C.S.E.: hon. asst. orthopædic surgeon, St. Helens Providence Free Hospital, Lancashire.
HART, C. B. L., M.R.C.S.: asst. M.O.H. and asst. school M.O., Rotherham.
HELME, VIVIEN, M.B. Lpool, D.OBST.: asst. M.O. for maternity and child welfare, Coventry.
HENSON, R. A., M.D. Lond., M.R.C.P.: asst. consultant physician, Maida Vale Hospital, London.
MCCAFFREY, MARGARET, M.B. N.U.I., D.C.H., D.P.H.: asst. M.O.H. and asst. school M.O., Bolton.
REYNOLDS, G. M., M.B., B.SC. Wales: asst. M.O. and asst. school M.O., Luton.
RUSSELL, J. T. R., M.D. Edin., F.R.C.P.E.: senior medical registrar, Edenhall Hospital, Musselburgh.
SCOTT, C. M., M.R.C.S.: appointed factory doctor, Barnet district, Hertfordshire.
STEPHEN, J. H., M.B. Aberd.: appointed factory doctor, Brill district, Buckingham.
TAYLOR, S. F., B.M. Oxfd, F.R.C.S.: asst. surgeon, King's College Hospital, London.
TERRY, ELSIE, M.D. Lond., M.R.C.O.G.: whole-time obstetrician and gynæcologist (consultant grading), East Fife group of hospitals.
THOMPSON, D. C., M.R.C.S.: senior house-officer, Queen Mary's Hospital, Roehampton.

Colonial Service:

DABROWSKI, JOZEF, M.B. Polish School of Medicine, Edin.: M.O., Federation of Malaya.
BENTSI-ENCHILL, K. K. O., M.B. Dubl.: M.O., Gold Coast.
EVANS, W. G., M.B. Wales: D.M.S., Sarawak.
GEMMELL, MIMA, M.B. Glasg., D.C.H.: M.O., Federation of Malaya.
GRASSO, PAUL, M.D., B.SC. Malta: M.O., Nigeria.
HLAWIEZKA, MARIA, M.B. Polish School of Medicine, Edin.: M.O., Federation of Malaya.
JACOB, GILLIAN, M.B. Camb.: pathologist, Uganda.
LISTON, J. M., M.B. Glasg., D.T.M. & H., D.P.H.: D.D.M.S., Hong-Kong.
MCFIE, JOHN, M.D.: M.O., Uganda.
MURCOTT, E. H., M.D. Edin., D.P.H.: Asst. D.M.S., Kenya.
NIBLETT, D. H., M.B. Calcutta: M.O., Sarawak.
POOLE, L. G., M.B. Lpool: senior M.O., Fiji.
RANKINE, T. B., M.B. Edin.: M.O., Federation of Malaya.
RUSH, S. V., M.R.C.S., D.O.M.S.: ophthalmic specialist, Nigeria.
STEWART, W. H., M.B.: M.O., Kenya.
THOMSON, G. M., M.D. Edin., M.R.C.P.E., D.P.H.: senior social hygiene officer, Hong-Kong.
THURSTON, E. W., M.B. Lond.: M.O., Tanganyika.

South Western Regional Hospital Board:

HACZKIEWICZ, STANISLAW, MED. DIP. Cracow: asst. chest physician (S.H.M.O.), North Gloucestershire clinical area.
JEANES, E. E [illegible] asst. venereologist (S.H.M.O.), Bristol, [illegible] Bath and South Somerset clinical areas.
STEEN, T. R., M.A., M.B. Camb., D.A.: consultant anæsthetist, Bristol clinical area.

Staffordshire County Council:

BRODBIN, PATRICK, L.R.C.P.I.: whole-time asst. M.O.
CLARK, SARAH, M.B. Belf., D.P.H.: whole-time asst. M.O.
KENNEDY, A. R., M.B. Manc., B.SC.: whole-time asst. M.O.
TATE, MILLICENT, M.R.C.S., D.P.H.: part-time asst. M.O.

Welsh Regional Hospital Board:

DAVIES, J. D., M.B. Edin., F.R.C.S.E.: consultant surgeon, Glantawe H.M.C.
FRY, PETER, M.R.C.S.: asst. psychiatrist (S.H.M.O.), St. Cadoc's Hospital, Caerleon, Monmouthshire.
HALEY, J. L., M.B., B.SC. Wales, D.A.: consultant anæsthetist, Glantawe H.M.C.
MARTIN, M. P. D., M.B. Edin.: asst. chest physician (S.H.M.O.), Montgomery and Merioneth T.B. area.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Notes and News

FIFTH WORLD HEALTH ASSEMBLY

THE assembly held its final sessions in Geneva last week. On May 15 Prof. C.-E. A. Winslow gave an address on the Economic Value of Preventive Medicine. He thought that W.H.O. had been wise in giving major emphasis in the past two years to simple and efficient measures, such as spraying with D.D.T. and the treatment of syphilis and yaws with penicillin, which gave dramatic and immediate results at minimum cost. But short intensive campaigns against individual diseases were, in themselves, demonstrations and not basic public-health programmes; they must be followed up or disease would regain the upper hand. In some parts of the world, notably in South-East Asia and the Near East, pressure of population demanded that attacks upon disease should be supplemented by efforts to limit excessive rates of increase. In the past year India had asked W.H.O. for expert counsel on methods of birth-control. Professor Winslow believed that improvement in health and prosperity may tend to promote a better balance of population. In countries with the highest economic status the excess of births over deaths was much less than in more crowded and less prosperous lands.

Population control was also discussed in committee. Dr. Karl Evang (Norway) proposed that an expert committee be set up to examine and report on the health aspects of the population problem. A second proposal by Dr. P. van de Calseyde (Belgium) suggested that from a strictly medical point of view demographic problems called for no specific steps by W.H.O. Dr. Evang felt that no criticism could be directed against W.H.O. for fulfilling a strictly technical function in this regard. There were also taboos in connection with food and nutrition, yet W.H.O. was carrying out successful programmes in this field. In fact, he said, people and governments would be relieved if W.H.O. took action in a cautious, scientific way on the subject. Dr. Evang's proposal was supported by the delegates of India, Ceylon, Sweden, Mexico, and the Philippines. Dr. C. G. Pandit, for India, stated that experts felt that overpopulation would bring disaster within 20 years unless adequate measures were taken. Technical guidance from a W.H.O. expert committee was necessary on this point and would not commit any country to actions which it might not wish to undertake. The delegations of Italy, Lebanon, Ireland, Spain, Costa Rica, and France supported the Belgian resolution. Dr. J. D. MacCormack, for Ireland, said that the countries faced with this terrible problem had his sympathy but what was needed was better economic and social conditions and more education. Birth-control, he warned, was unsound and led to abuses, and calling an expert committee might give rise to great opposition if it took a line objectionable to so many persons. Dr. E. J. Aujaleu, for France, suggested that a decision on this point should be left to the United Nations itself, and that W.H.O. could then act on a clear mandate.

It was decided after a long debate that no further action should be taken.

THE ROYAL SOCIETY

OF the many remarkable exhibits at the society's conversazione on May 22, the one which may prove of greatest medical significance was the story, told by the National Institute for Medical Research, of the extraction from the sisal plant of a substance from which cortisone can be made. Sisal is grown in enormous quantities in Tanganyika, Kenya, and elsewhere for its rope-making fibres. This substance, hecogenin, is only one of several possible starting-points on the way to cortisone; Mexican yams, West African arrow-poisons, and other exotic things also contain compounds with promising formulæ; but hecogenin must be reckoned one of the favourites because of the cheapness and relative ease with which it can be extracted from sisal-juice, a hitherto useless by-product in the preparation of the fibres. The transformation is not a simple one: the hecogenin molecule must be rearranged and modified by some twenty chemical steps to turn it into cortisone, but it has been done in the laboratory. If the chemistry proves industrially feasible, the search for abundant and cheap sources of cortisone may be at an end.

Also from the institute was an apparatus for the continuous culture of bacteria in the steady state. A growing culture was mixed and aerated in a rotating vessel and continually diluted with fresh medium, while the volume was kept constant by suction. The rate of dilution and the rate of growth were such that the system was in a self-regulated steady state.

The Blood Group Reference Laboratory of the Medical Research Council showed some excellent maps and diagrams illustrating the distribution of blood-groups and other genetically simple characters.

It was difficult to get near the "flying spot" microscope from University College; for its television screen attracted a large audience. This instrument has greater contrast and resolution to show for its complexity, as the programme featuring *Schistosoma mansoni* certainly proved.

The Zoological Society of London brought along some rar tropical rodents—some attractive, some repulsive. The delicate and charming African pygmy mouse kept a twinkling eye out for any stray schoolboys who might add him to thei matchbox menagerie, while his mate looked unimpressed a being described as the minimum size possible for a mammal The formidable African pouched rat was asleep, apparently untroubled by the "aberrant earwig" that lives in its fur. The Marine Biological Association of the United Kingdom caught some specimens for the evening; the common prawn is very unappetising in life, and the hairy porcelain crab is a minor monster. The polychæte worm, chætopterus, was confined in a box with peepholes but no slot for the penny. Irritated by this and other stimuli, it glowed a pleasant blue.

ANNUAL REPORTS FROM HOSPITALS

LAST year the Select Committee on Estimates[1] recommended that "each Hospital Management Committee should issue, as soon as the year's accounts are available, a statement in narrative form, giving a general description of the Committee's activities during the year and including the main operational statistics and the salient figures in the accounts." This recommendation has been accepted by the Ministry of Health (R.H.B.[52]53), which also states that figures or audited accounts may be published before the annual summary accounts are presented to Parliament. The Ministry also emphasises the importance, as a means of stimulating local interest, of holding annual meetings open to the public and of issuing annual reports. These reports, the Ministry suggests, should cover the activities of boards or committees as a whole; and normally separate reports should not be produced for the individual hospitals of a group.

GREAT ORMOND STREET CENTENARY

THE Hospital for Sick Children is vigorously celebrating its 100th birthday. The occasion on May 26 was called a clinical meeting, but it could be better described by saying that the staff were clinically at home. Visitors made their way from ward to ward and department to department taking their choice from an abundance of interesting cases and demonstrations; for a week would have been too short a time to see everything properly.

Dr. Wilfrid Sheldon had arranged a demonstration to show by chart and graph how research into cœliac disease had finally led to the implication of the gluten fraction of wheat-flour. And elsewhere Prof. Alan Moncrieff showed a cœliac child whose weight had remained at about 33 lb. from the age of four to eleven, but who then gained over 20 lb. in four months on a high-protein, low-fat, and pure starch (gluten-free) diet. Dr. David Lawson had traced the records of a man operated on at Great Ormond Street as a child in 1905 for removal of a tuberculoma of the cerebellum. This ex-patient came along to show how well he had been since. It would be interesting to know of any earlier and equally successful excision of an intracranial tumour. Children recovering from neonatal hepatitis were discussed by Dr. G. H. Newns. It is important to distinguish this condition, in which the outlook is usually favourable, from congenital obliteration of the bile-ducts; nearly always this can be done by repeated examination of the stools for stercobilin. Dr. A. P. Norman's series of children with fibrocystic disease of the pancreas included three pairs of siblings, and showed how these patients can flourish after they have been helped over the early stormy stages. Dr. J. C. W. Macfarlane described the new antithrombin test which can establish the diagnosis in a high proportion of cases of fibrocystic disease. A small boy, a patient of Dr. B. E. Schlesinger, was given to biting the heads off his toy soldiers and swallowing them; he developed chronic ad poisoning with encephalopathy, but he is now cured of oth disease and diet.

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[1] Eleventh report from the Select Committee on Estimates. H.M. Stationery Office, 1951. See *Lancet*, 1951, ii, 573, 590.

In the operating-theatre Mr. James Crooks demonstrated e Great Ormond Street technique for tonsillectomy, riginally devised in 1910 by Mr. George Waugh, surgeon to e hospital. Children with Hirschsprung's disease were eing treated in the surgical wards by Mr. Charles Donald; nd Dr. Martin Bodian included specimens of the disease mong his pathological exhibits.

On May 27 the Princess Royal laid the foundation stone f the new outpatient building.

EMERGENCY BED SERVICE

The report of the Emergency Bed Service for the year nded March 31, 1952, remarks that after May, 1951, the onthly totals of applications for admission of general acute ases to hospital fell for the first time since the National ealth Service was introduced in 1948; and the admission-ate of 88·6% was higher than in any year since the service egan. The decline in applications was, however, almost ntirely in respiratory disease. There was a small decline n applications for acute surgical cases which, says the report, ay indicate that practitioners were finding it somewhat less ifficult to arrange admission of such cases direct to hospital. here was also a great reduction in applications for cases of nfectious disease—from 17,445 in 1950–51 to 12,088 in 951–52. The total number of applications for general cute, infectious, and chronic sick cases was 62,861, compared ith 71,214 in the previous year—a decrease of 11·7%.

AMENITY AND PRIVATE BEDS IN HOSPITALS

The Ministry of Health, in a circular to hospital authorities RHB[52]54), asks boards and committees to keep constantly nder review the extent to which section-4 (amenity) beds re being used, "and in the light of this to consider whether urther measures are necessary to secure their full use." The ircular suggests that there will be continuing need to publicise he existence of such beds. "One of the most effective methods s to make routine arrangements for each prospective patient o be told about the existence of these beds, either personally hen admission is being arranged or by means of any written otice which is sent to patients. . . . Misunderstandings are voided if at the same time it is made clear that there can be o guarantee that a Section 4 bed will necessarily be available t the time of admission."

With regard to section-5 (private) beds, "the Minister onsiders that arrangements should be made to ensure that hose beds which are not normally occupied by paying patients re used for other patients." The circular suggests that the umber of both section-4 and section-5 beds should be adjusted according to the demand for each; and it asks hospital boards to submit by Jan. 31, 1953, a statistical return showing how the beds in each of these groups have been used in the last six months of this year.

PRACTITIONERS' ACCESS TO MATERNITY UNITS

In the *Hospital and Social Service Journal* this week, Mr. S. G. Hill, secretary of the Northampton and District Hospital Management Committee, suggests that management committees which oppose access by general practitioners to maternity units have either not thought out the idea very carefully, or "are really afraid of losing a little function, whatever other reasons they give for their opposition." Mr. Hill writes from experience, for general practitioners have been able to deliver their patients in a maternity home in the Northampton area almost since the start of the National Health Service; and a similar scheme is to be started in Northampton itself.

Mr. Hill observes that normally patients admitted to maternity units prefer to be delivered by their own family doctor. Many management committees, however, see insuperable objections to such an arrangement. The committee may, for instance, think that it would thus lose control over the unit. This Mr. Hill denies. The general practitioners should, at the start of the scheme, understand that the unit remains the over-all responsibility of the committee, administratively through its secretary and clinically through the consultant obstetrician. The consultant obstetrician should decide which practitioners are given access to the unit; but, to avoid any suggestion of personal interference, an appeal should lie to the management committee from any practitioner who fails to gain access or whose name is removed from the list. The committee may also fear that general practitioners will tend to admit cases on considerations unrelated to real social need for a hospital bed. "Again, this fear is completely groundless, as the final allocation of beds to patients should be decided entirely by the Local Health Authority, upon assessment of the relative social needs of patients seeking admission." The only substantial objection to access by general practitioners is that this may be inconsistent with the recognition of the unit as a part-2 training-school for midwives; but any difficulty here, Mr. Hill says, can be overcome with good faith and apt administration.

NAMING INSECTICIDES

The many new compounds used in medicine, agriculture, and industry to control insects and other pests have some confusing names. The British Standards Institution has therefore prepared a list of recommended names to replace the cumbersome chemical ones and the ambiguous shortened forms that have become current. The names proposed will not conflict with those of proprietary compounds; they are intended for day-to-day use in identifying the active ingredients in the various preparations. Initials or numbers have been avoided, except in the case of a substance that has become well known by such a name. Copies of the standard may be had, price 2*s.* 6*d.*, from the sales branch of the institution at 24, Victoria Street, London, S.W.1.

DISCOVERY OF ANAPHYLAXIS

On May 10 the 50th anniversary of the discovery of anaphylaxis by the late Prof. C. R. Richet and by Prof. Paul Portier was commemorated in Paris. Professor Portier, who spoke at the meeting, described how their systematic studies on board ship off the Cape Verde Islands led to the new phenomenon which he named anaphylaxis to express the opposite to a protective effect or prophylaxis. The distinguished son of a distinguished father, Prof. Charles Richet said that although the treatment of allergic complaints had advanced but little since his father's time, Dr. Halpern's work was a reminder that antihistaminic drugs, which constitute the only real advance, were first investigated and used in France. Prof. Pasteur Vallery-Radot reviewed the clinical applications of the discovery. Sir Henry Dale, O.M., who was also present, spoke on the Mechanism of Anaphylaxis.

University of London

Dr. P. C. C. Garnham has been appointed to the chair of medical protozoology at the London School of Hygiene and Tropical Medicine from Oct. 1.

Dr. Garnham graduated M.B. Lond. from St. Bartholomew's Hospital in 1923 and took his D.P.H. the following year. Soon afterwards he was appointed M.O. for Kumasi in Kenya. In 1928 he took his M.D. in tropical medicine and in 1931 a diploma in malaria at the University of Paris. Later he became senior parasitologist for Kenya. After the late war he returned to this country to take up his present appointment as reader in parasitology at the London School of Hygiene. At the 3rd International Congress of Tropical Medicine and Malaria in Amsterdam in 1938 he spoke on the epidemiology of *Anopheles funestus* malaria, and he has also published a paper on the Developmental Cycle of *Hepatocystes kochi* in the Monkey Host. He was a member of the team which demonstrated the existence of a pre-erythrocytic cycle in mammalian malaria.

Dr. J. A. B. Gray has been appointed to the readership in physiology tenable at University College from Oct. 1.

Dr. Gray studied medicine at the University of Cambridge and at University College Hospital where he held a house-appointment after he graduated M.B. in 1942. Since then he has worked at the National Institute for Medical Research in the department of physiology and pharmacology. His published work includes a paper on the Initiation of Impulses from Mesenteric Pacinian Corpuscles.

Royal College of Physicans of London

On Thursday, July 3, Sir Rudolph Peters, F.R.S., will deliver the Bertram Louis Abrahams lecture. He has chosen as his subject the Puzzle for Therapy in Fluoracetate Poisoning. On Tuesday, July 15, Mrs. Margaret Hill is to give the F. E. Williams lecture on the Dangers of Chronic Inactivity in Old Age. Both lectures will be held at 5 P.M. at the college, Pall Mall East, S.W.1.

Royal College of Surgeons of Edinburgh

At a meeting of the college held on May 21, with Prof. Walter Mercer, the president, in the chair, the following were admitted to the fellowship:

Suleiman Abul-Husn, D. H. Biggs, C. B. Cornish, R. P. Cumming, B. M. de Saxe, Amy Dhunjibhoy Engineer, Wilfrid Grundill, Rahman Habib-Ur, J. D. Hennessy, Jagat Singh Karanwal, Alexander Marshall, Jittoo Manoo Mehta, A. H. Moore, H. D. Rawson, T. F. Redman, A. E. Rublack, D. P. Short, G. A. Silley, Leslie Simon, Perin Ratansha Toddywala, D. M. Whitley.

University of Leeds

Dr. C. L. Oakley has been appointed to the Brotherton chair of bacteriology.

Dr. Oakley was educated at Westminster City School and Chelsea Polytechnic, where he was appointed demonstrator in zoology in 1926. Meanwhile he continued his medical studies at University College and University College Hospital, where he graduated M.B. in 1930. For the next three years, with a Graham scholarship in pathology, he worked under A. E. Boycott at U.C.H. Medical School. In 1933 he became experimental pathologist at the Wellcome Research Laboratories, and in 1947 he was promoted to be head of the immunology and experimental pathology department. He was elected a fellow of University College in 1950.

Miss Ursula M. Lister has been appointed senior lecturer in obstetrics and gynæcology, and Dr. J. O. Laws has been appointed Louisa and Elizabeth Ward fellow.

On July 9, on the occasion of the holding in Leeds of the thirteenth British Congress of Obstetrics and Gynæcology, the honorary degree of doctor of laws will be conferred on Prof. Albert H. Aldridge, chief surgeon to the Woman's Hospital in the State of New York and clinical professor in obstetrics and gynæcology at Columbia University, New York; Prof. M. A. Bouwdijk Bastiaanse, head of the department of obstetrics and gynæcology at the University of Amsterdam; and Sir Eardley Holland.

With the sum of £1930 which has been subscribed by friends of Emeritus Professor Matthew Stewart it is proposed to present to the university a bronze plaque of Professor Stewart, and to endow a Matthew Stewart lectureship.

Research Chair in Ophthalmology

The League of Friends of the Royal Eye Hospital, London, have collected £25,000 towards the £100,000 which they need for the research chair in ophthalmology which they propose to endow.

Hunterian Society

The gold medal of the society has been awarded to Dr. G. M. Temple Tate, of Mansfield, and a proxime accessit award to Dr. M. Solomon, of Bootle.

Nutrition Society

All inquiries about meetings of this society should now be sent to Mr. R. J. Allen, Monkhouse & Glasscock Ltd., Snowsfields, London, S.E.1, who has been elected programmes secretary in succession to Mr. G. H. Bourne, D.SC.

Conference of Prison Medical Officers

The annual conference of prison medical officers was held at the Home Office on May 23. Dr. Desmond Curran and Dr. Maurice Partridge spoke on Psychopathic Personality; and during the afternoon Dr. B. M. Tracey, Dr. J. L. leC. Walker, Dr. T. Christie, and Dr. P. V. L. Epps were the opening speakers in a symposium on Arson.

Conference on Hospital Planning

The National Council of Nurses of Great Britain and Northern Ireland are holding an open conference on Sept. 2 at the Royal Institute of British Architects, 66, Portland Place, London, W.1. The speakers will include doctors, nurses, and architects. Tickets (3*s.* for non-members, 2*s.* 6*d.* for members) may be had from the executive secretary of the council, 17, Portland Place, London, W.1.

Conference on Maternity and Child Welfare

The main subject chosen for discussion at this conference, which the National Association for Maternity and Child Welfare is holding at Church House, Westminster, from June 25 to 27, is the Wastage of Child Life before and after Birth. The speakers will include Dr. Margaret Hadley Jackson, Prof. Dugald Baird, Prof. T. McKeown, and Dr. H. Marshall Scott.

British Association of Urological Surgeons

The annual meeting of the association will be held in London at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2, from June 26 to 29. The programme includes a discussion on the Late Results of Ureterocolic Anastomosis to be opened by Mr. Arthur Jacobs and Mr. W. B. Stirling. There will also be a joint meeting with the section of urology of the Royal Society of Medicine when Dr. E. M. Darmady, Dr. G. M. Bull, and Mr. Ashton Miller will open a discussion on the treatment of anuria.

Reinstatement in the National Health Service

The N.H.S. Tribunal have considered the application of Dr. Archibald Blair for reinstatement to a medical list. As a year has elapsed since his original exclusion they have agreed that his name may now be included in the medical list of any executive council.

American Academic Grants

The American Embassy, the English-Speaking Union, and the United States Educational Commission in the United Kingdom are offering grants to assist British graduates to attend universities in the United States of America during 1953–54. Further information may be had from Mrs. D. R. Dalton, B.A., Universities Department, The English-Speaking Union, 37, Charles Street, Berkeley Square, London, W.1.

Birth, Marriage, and Death Certificates

From July 1 the charges in England and Wales for ordinary certificates of births, marriages, and deaths, will be increased from 2*s.* 6*d.* to 3*s.* 9*d.*, and for short birth certificates from 6*d.* to 9*d.* There will be no increase in the fees for the special cheap certificates (6*d.* and 1*s.*) of births, marriages, or deaths prescribed under Acts of Parliament. The registration of births, marriages, and deaths will continue to be free.

New N.I. Certificate

The number of kinds of prescribed certificate of incapacity has been reduced from five to three under new regulations made by the Minister of National Insurance (S.I. 1952, no. 992). The special intermediate certificate and the intermediate convalescent certificate are no longer necessary, as additional details have been included in the new intermediate certificate. The new first certificate will enable a doctor to give a single certificate for an illness which lasts only a few days, instead of two certificates as hitherto. Copies of the new certificates will be distributed by executive councils as stocks of the old certificates are used up. A leaflet (M.C.1) explaining the use of the new certificates is being sent to doctors.

Exhibition of Medical Illustration

On Saturday, June 14, at 3 P.M., Sir Henry Cohen will open an exhibition of photography and art in medicine at B.M.A. House, London, W.C.1. The exhibition, which is presented by the medical group of the Royal Photographic Society and by the Medical Artists' Association of Great Britain, will remain open till June 28 (10 A.M. to 5 P.M.; 8 P.M. on Wednesday). Films will be shown at 7 P.M. on Thursdays, June 19 and 26, in the lecture-theatre of Messrs. Ilford, Tavistock House North.

The exhibition will later be transferred to Manchester, and will be opened on Saturday, July 5, at 11.30 A.M., by Sir Geoffrey Jefferson, F.R.S. It will be open from July 7 to 19 (10 A.M. to 6 P.M.; 1 P.M. on Saturdays) in the histological laboratory of the medical school, Manchester University.

The tenth edition of the Orthoptists' section of the National Register of Medical Auxiliary Services has been published. Copies will be sent free to doctors, hospitals, and local authorities, who apply to the secretary of the board, B.M.A. House, Tavistock Square, London, W.C.1.

Prof. John Beattie, Dr. J. F. Loutit, Dr. H. M. Sinclair, and Dr. E. L. Sturdee have been appointed officers of the Order of Orange Nassau.

At the invitation of the Finnish Medical Board and under the auspices of the British Council, Prof. D. R. MacCalman is visiting Finland from May 15 to 30.

Prof. B. W. Windeyer has been appointed honorary consultant in radiotherapy to the Royal Air Force.

The proceedings of the Colloquium on the Chemotherapy of Tuberculosis, held by the Medical Research Council of Ireland in July, 1951, have been published on behalf of the council by the Parkside Press Ltd., 43, Parkgate Street, Dublin.

The Brazilian journal *Arquivos de Clinica* has been absorbed by its contemporary *Arquivos Brasileiros de Medicina.*

Cancer, a journal of the American Cancer Society, is now distributed throughout Great Britain and the Commonwealth by Messrs. E. & S. Livingstone Ltd., 16–17, Teviot Place, Edinburgh, 1. The annual subscription is £4 10*s.*

Evans Medical Supplies Ltd. have moved their London offices and workshops to Ruislip, Middlesex (Ruislip 3333).

THE COURSE OF ANTERIOR HYPOPITUITARISM *

DOUGLAS HUBBLE
M.D. Lond., M.R.C.P.

PHYSICIAN, DERBYSHIRE ROYAL INFIRMARY, DERBY CITY HOSPITAL, AND DERBYSHIRE HOSPITAL FOR SICK CHILDREN

THE late Sir Walter Langdon-Brown first used the phrase: "the pituitary is the leader of the endocrine orchestra." At that time—in 1935—there were but vague and imprecise outlines of the disorders which resulted from diminished pituitary function; and although knowledge of them has steadily accumulated through the work of physicians, of biochemists, and of pathologists, yet clinical observation can still do much to clarify these deviations of human physiology.

The adenohypophysis or anterior pituitary, with which this paper is concerned, certainly secretes six, and possibly seven, separate hormones. The sex hormones are three—the follicle-stimulating hormone (F.S.H.), the luteinising (L.H.) or interstitial-cell-stimulating hormone (I.C.S.H.), and the luteotropic (L.T.H.) or lactogenic hormone. One hormone, the growth factor (G.H.), operates directly on tissues, while the remaining two, the adrenocorticotropic (A.C.T.H.) and the thyrotropic (T.S.H.) act by the stimulation of another endocrine organ. While these six hormones have been obtained as homogeneous proteins, the presence of other hormones is debatable; but a case can be made for the secretion of an anti-insulin hormone, which, however, is probably identical with the growth hormone (Young 1951).

There are but two secreting cells in the anterior pituitary—the eosinophils and the basophils—so that between them they must be responsible for the production of these seven hormones. It is usually agreed that the eosinophils produce the growth hormone and the basophil cells produce the follicle-stimulating hormone. While it is further assumed that the eosinophils also produce the luteinising and the lactogenic hormones, and the basophils secrete the adrenocorticotropic and the thyrotropic hormones, Albright and Elrick (1948) have recently argued that the basophil cells produce F.S.H. and possibly also L.H. and that all the remaining hormones are produced by the eosinophil cells.

There are now many conditions in which some diminution of anterior pituitary function can be proved or reasonably assumed. Eleven examples of anterior hypopituitarism will now be described to establish certain principles which regulate the order of disappearance of the various functions of the adenohypophysis. These cases illustrate what happens to the other members of the endocrine orchestra when the *maestro* is defective, depressed, undernourished, obliterated from without, or disintegrated from within.

Genetic Hypopituitarism

It may now be regarded as established that either a deficiency or total absence of gonadotropins can occur as a developmental defect of the anterior pituitary. Hypogonadism is the result, both in men and in women; and while this type does not form a large proportion of all cases of hypogonadism, yet it is by far the commonest clinical syndrome in which a primary deficiency of any of the anterior pituitary hormones has been demonstrated.

Howard and his colleagues (1950) found 19 of these cases in their investigation by endocrine assay and testicular biopsy of 141 men with testicular deficiency. They divided them into three groups. In the first (5 patients) there was a primary lack of F.S.H. In the second (3 patients) they assumed the existence of a primary defect in L.H., in addition to F.S.H., because adrenal androgenic function was absent, as evidenced by deficiency both of urinary 17-ketosteroids and of pubic and axillary hair. The remaining 11 cases showed a quantitative diminution in gonadotropin, but there was evidence in them of a varying degree of tubular stimulation.

Similar hypogonadal groups have been established in women, although in them the gonadal status is usually indirectly assessed since ovarian biopsy has not been so commonly practised as has testicular biopsy. The essential diagnostic investigation is the laboratory assay of urinary gonadotropins; for these are reduced or absent in hypopituitarism but are normal or increased in primary gonadal deficiency. It should be emphasised that these gonadotropic deficiencies occur in the absence of any evidence of pan-hypopituitarism. They are, in fact, selective deficiencies of gonadotropins. It should be noted also that they occur in the absence of any recognisable ætiological factor.

It is possible that some instances of cretinism may prove to be due to a congenital deficiency of the thyrotropic hormone. When the thyrotropic hormone has been assayed in cretinism it has been reported to be present in excessive amounts—as would be expected if the condition were due to thyroid failure. Improved methods of bio-assay are now available, and De Robertis (1948) reported that the thyrotropic hormone was practically absent in a cretin aged 28; but this was after two months' intensive treatment with desiccated thyroid and at a time when the patient's basal metabolic rate was +38%. Thyroid administration may have suppressed the secretion of the thyrotropic hormone.

A boy aged 11 with cretinism was included in a recent series of patients with thyroid disorder investigated by thyrotropic hormone assay by D'Angelo et al. (1951), and in his serum no T.S.H. could be demonstrated. It appears probable that cretinism will soon be established as of at least two types—in one of which there is a selective deficiency of T.S.H. and in the other a primary failure of the thyroid gland.

Since the adrenal cortex is essential for survival and is itself dependent on A.C.T.H. for its continued function, it appears probable that the individual would not long survive in the presence of a selective deficiency of A.C.T.H. Certainly no case of Addison's disease due to a genetic defect of A.C.T.H. production has been reported. Primary and selective deficiency of the growth hormone undeniably occurs, but much less frequently than does a deficiency of gonadotropins.

Dwarfism and hypogonadism are often conjoined primary defects, but sometimes hypopituitary dwarfism occurs without hypogonadism. Well-authenticated examples of selective deficiency of the growth hormone are rare, but Hewer (1944) made a post-mortem examination on a female dwarf aged 73, whose height was 3 ft. 11 in. and who had produced one female child. He found only 0·2% of eosinophil cells present in counting 2000 cells in the anterior pituitary.

While these deficiencies of the growth hormone may be associated with some unrecognised environmental pathogenesis, some of them probably depend on a genetic defect. Smith and MacDowell (1931) described an inherited deficiency of eosinophil cells in a strain of dwarf mice. I have reported hypopituitarism in two male first cousins (Hubble 1951):

The boy, aged 8 years, is a hypopituitary dwarf in whom no other anterior pituitary defect can be discovered, although it is not yet possible to define his sexual development; while his first cousin, aged 20, is of eunuchoid habitus of hypopituitary origin. The man's height is normal, although his skeleton shows osteoporosis with delayed epiphyseal union (androgen deficiency). His gonadotropin output is less than 6 M.U. in 24 hours, while his testicular biopsy shows an absence of Leydig cells and prepubertal tubular development.

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* Based on a communication made to the Association of Physicians in Glasgow, in May, 1951.

Since the publication of these cases, I have learnt that the man is not only the boy's first cousin, but also his mother's half-brother.

SUMMARY

Genetic hypopituitarism commonly affects the gonadotropins, and much less frequently the growth hormone. These deficiencies are usually selective but may occur together. A developmental selective deficiency of the adrenocorticotropic hormone has not yet been described, but evidence is now accumulating that a selective deficiency of T.S.H. is responsible for some cases of cretinism.

Nutritional and Psychogenic Hypopituitarism

These two causes of functional depression of the adenohypophysis are considered under one heading because in certain clinical conditions, such as anorexia nervosa, malnutrition and the abnormal psychic state are joint factors in pathogenesis which it is sometimes impossible to separate.

That a functional hypopituitarism does occur must now be universally accepted. The conclusion that malnutrition induces it depends on both clinical and experimental evidence; that it also occurs in abnormal psychic states is supported by clinical and laboratory examination.

In undernourished animals the gonadotropins are first and most markedly affected of all the anterior pituitary hormones. Evans and Bishop (1923) first showed in rats that a diet which was adequate for growth was quite inadequate for reproduction. Maddock and Heller (1947) have shown that the first effect is a failure of secretion of gonadotropins, while the later result is a failure of production. Samuels's (1948, 1950) experiments in rats have proved that any diets with a negative nitrogen balance will produce atrophy of the seminal vesicles and the prostate; and he showed also that in the diet of the rat tryptophane is essential for the synthesis of gonadotropins.

Experimental evidence indicates that defective diets not only produce a deficient response of the tissues to the growth hormone (Gordan et al. 1948) but also reduce the production of growth hormone to below optimal levels. For example, Li and his colleagues (1949) showed that when animals were placed on defective diets, the growth of the skeleton was retarded; but, administration of growth hormone, despite the maintenance of the same defective diets, led to an increased rate of growth and reduced nitrogen excretion. D'Angelo (1951) has demonstrated that in rats and mice the secretion of thyrotropic hormone is significantly reduced in acute starvation; but several workers have shown that although the thyroid gland is reduced in size in chronic malnutrition, the histological changes in the gland are not marked. The pituitary-adrenal system in rats, as Sayers and his co-workers (1950) have shown, is maintained despite severe protein deficiency.

A group of rats was fed on a protein-free diet until their [illegible] reduced to half their normal levels. [illegible] of a control group fed on normal [illegible] rats from both groups were then [illegible]ss and killed 24, 48, and 72 hours [illegible] of the pituitaries and the amount [illegible] cholesterol in the adrenals were approximately the same in both groups.

It appears that chronic mild undernutrition will eventually produce adrenocortical atrophy in rats. Selye (1940) found that this occurred only if the diets [illegible] value with a dispro- [illegible] tein content. [illegible] o diets, the gonado- [illegible] profoundly disturbed, [illegible] adrenocorticotropic hormones may be deranged in some degree.

Malnutrition which is sufficiently severe and prolonged to affect the formation of anterior pituitary hormones can occur in such diseases as anorexia nervosa and cœliac disease. Medical officers in prison camps during the late war found that amenorrhœa and reduced fert in women (Sydenham 1946), and testicular atrophy loss of sexual function in men (Jacob 1948), resulted defective diets. Sydenham found that on a diet containing 45 g. of protein daily, more than half of the imprisoned women developed amenorrhœa; and when, for five months, a ration of tinned meat improved considerably their protein intake, menstruation recommenced in all but 6 of the 234 women.

It is not easy to deduce from animal experiments the exact cause of the failure of sexual function and of growth which occurs in malnutrition, and the problem is even more complex in man. For example, defective diets will obviously cause impaired growth through an inadequate supply of nutrients—an effect quite distinct from underproduction of the growth hormone. Again, psychogenic depression of anterior pituitary hormones undoubtedly occurs; and the debatable importance of a mental state versus malnutrition as ætiological factors in the suppression of sex function is well demonstrated in anorexia nervosa (vide infra). Sydenham infers that the early onset of amenorrhœa in some of her patients was due to emotional causes, because it occurred before the protein deficiency could reasonably be assumed to be effective. It is generally accepted that amenorrhœa may be induced by emotional stimuli which are mediated by the hypothalamus ("hypothalamic amenorrhœa"). The evidence for this has recently been summarised by Bowman and Reifenstein (1950).

The following cases illustrate the effects of malnutrition and abnormal psychic states on anterior pituitary function.

SEX HORMONES

Anorexia Nervosa

Case 1.—*A spinster, aged 23, an illegitimate child of a* hospital cook in Aberdeen. Amenorrhœa had been absolute for three years, but anorexia had been present in some degree since she was 15. The determining psychological situation was resentment against her mother and her legitimate step-sister. Her weight on admission to hospital was 4 st. 10 lb. Her urinary output of 17-ketosteroids was 9·6 mg. in twenty-four hours, while no gonadotropic hormones and no œstrogens were detected in her urine. The fasting blood-sugar was 85 mg. per 100 ml., and the insulin-sensitivity test (fig. 1) was within normal limits (100%, 50%, 60%, 74%, 86%).† The number of eosinophils was always below 50 per c.mm., and the Robinson-Power-Kepler test was negative. "Hibernation" hirsuties was marked and sexual hair was abundant, despite the absence of œstrogens.

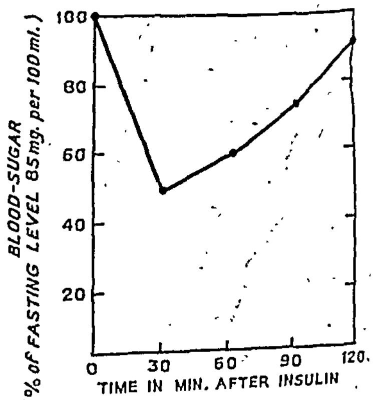

Fig. 1 (case 1)—Anorexia nervosa. Normal insulin-sensitivity curve.

Case 2.—This case was unusual in that anorexia nervosa developed in a woman aged 23 who had borne one child. On admission (fig. 2) she was 5 st. 8 lb., having lost 2 st. in the previous thirteen months. She had four normal periods after the birth of her first child, but then had amenorrhœa and loss of libido for two years. Appetite failed six months after her periods ceased, and the determining psychogenic stress appeared to be the fear of domestic and family responsibility in a woman who is excessively dependent on her mother. The urinary 17-ketosteroids were 12·6 mg. in twenty-four hours, but she had no gonadotropin output and there was no œstrogen in the urine. The fasting blood-sugar was 96 mg. per 100 ml. and the insulin-sensitivity test (fig. 3) showed values of 100%, 48%, 64%, 70%, 90%. The eosinophils were reduced from 189 to 17 per c.mm., four hours after the injection of 25 mg. of A.C.T.H.—a normal oxysteroid response. There was no evidence of depression of thyroid or adrenocortical function.

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† Insulin-sensitivity tests are here expressed as a percentage of the fasting blood-sugar, which represents 100% (Russell Fraser 1948).

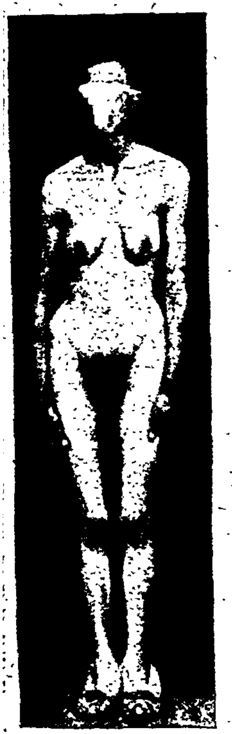

Fig. 2 (case 2)—Anorexia nervosa.

J. H. Sheldon (1939) was the first to clarify the relation of hypopituitarism to anorexia nervosa and its differentiation from Simmonds's disease; and all subsequent work has confirmed his hypothesis. Sheehan (1948) has demonstrated that emaciation is not a cardinal feature of his syndrome (vide infra). The occurrence of amenorrhœa in nervous disorders has been attributed by Reifenstein (1946) to a block of the normal continuous stream of impulses from the hypothalamus to the anterior pituitary which results in the production and discharge of luteinising hormone. He has called this "hypothalamic amenorrhœa" and it results in absent or defective œstrogen output associated with a normal output of urinary gonadotropins. McCullagh and Tupper (1940) found that 11 of 13 patients with anorexia nervosa showed a substantial decrease in œstrogen excretion, while 10 out of 18 showed a diminution or absence of gonadotropin output. In 7 out of 9 patients with anorexia nervosa MacGregor found neither œstrogen nor gonadotropin in the urine.

These 2 patients (cases 1 and 2) both demonstrate, by the absence of urinary gonadotropins, that hypopituitarism was in them the cause of the amenorrhœa. In case 1 the anorexia preceded the amenorrhœa by some years, but in case 2 the amenorrhœa preceded the anorexia by six months. J. H. Sheldon tells me that in 24 out of 86 recorded cases of anorexia nervosa, amenorrhœa preceded the anorexia. It is clear that in such patients hypothalamic intervention and not malnutrition is then responsible for the amenorrhœa. It may be that when a diminished output of gonadotropins occurs in anorexia nervosa, this is the result of malnutrition; and although it has been stated that gonadotropin deficiency develops late in anorexia nervosa, this is not altogether borne out by case 2. It may be concluded that amenorrhœa may result either from a psychogenic depression or from malnutrition, and in anorexia nervosa these two factors may combine to produce it.

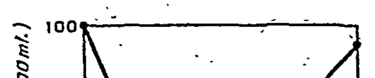

Fig. 3 (case 2)—Anorexia nervosa. Normal insulin-sensitivity curve.

When diets again become adequate, the restoration of sexual function is remarkably rapid. In the war-time patients of Jacob and Sydenham, a few weeks on full diet sufficed for complete recovery. W. Sargant (1951, and personal communication) relates that in 2 women with long-standing anorexia nervosa treated by leucotomy, menstrual function was restored in three and nine months, but in these intervals the patients had gained 42 lb. and 38 lb. It is apparent that in anorexia nervosa the restoration of menstrual function waits upon normal nutrition.

There is no evidence that other pituitary functions are depressed in anorexia nervosa. In these 2 patients thyroid function, as judged by clinical and laboratory examination, was normal, and adrenocortical function, as judged by repeated eosinophil examinations, by the renal response to a standard water-load, by estimations of 17-ketosteroid excretion, and by the sustained growth of sexual hair, was also normal. This agrees with the finding of T. R. Elliott in 1914 that the adrenal glands are well preserved in anorexia nervosa, and Jackson's experimental observation (1925) that the size of the adrenals was increased in acute starvation in animals. Thorn et al. (1950) state that they have observed patients with severe anorexia nervosa exhibit a low 17-ketosteroid excretion, suggestive of decreased adrenocortical activity, and they conclude that this low level of adrenal activity is secondary to anterior pituitary hypofunction. They record that in 2 such patients great clinical improvement resulted from A.C.T.H. therapy. In 2 of my cases, not detailed here, the 17-ketosteroid excretion was consistently below 4 mg. in twenty-four hours, but a reduced excretion of 17-ketosteroids is not of itself sufficient evidence of A.C.T.H. depression in the absence of evidence of other adrenocortical deficiency, and from the evidence already reviewed it appears improbable that adrenocortical depression is a usual finding in anorexia nervosa. It may be that this deficiency of adrenal androgens is dependent on L.H. deficiency and not on interference with A.C.T.H. (vide infra). A good response to A.C.T.H. therapy can hardly be held to establish Thorn's hypothesis.

Cœliac Disease

The occasional persistence of cœliac disease into adult life provides an opportunity for assessing the effect of malnutrition on sex function.

Case 3.—A spinster aged 38. First seen more than three years ago and observed continuously since. She gave a history of repeated attacks of diarrhœa since childhood. Menses had commenced at the age of 15 and occurred every three to four months, lasting no more than a day or two, with slight loss. Amenorrhœa was absolute from the age of 37. Her presenting symptoms were pallor, shortness of breath and pains in the back and limbs. Her height was 4 ft. 8 in. Her bones showed generalised osteoporosis, most evident in the thoracic spine. Serum-calcium was 8·2 mg. per 100 ml. and serum-phosphorus 3·2 mg. The total fat on three examinations was between 33% and 48% of the dried fæces, representing 12·4 to 16·8 g. of fat in twenty-four hours. The barium meal showed an abnormal mucosal pattern in the small intestine with clumping of barium. The serum-proteins were 4·6 g. per 100 ml. Anæmia was considerable: hæmoglobin 7·2 g. per 100 ml. and red cells just under 3 million per c.mm. The red cells were hypochromic, but the red-cell series in the bone-marrow showed 10% of megaloblasts. Pubic and axillary hair was sparse. The urinary excretion of 17-ketosteroids was 2·5 mg. in twenty-four hours (1949) (3·5 mg. in 1950, 5·0 mg. in 1951). Gonadotropin and œstrogen output in 1949 and 1950 was reported to be nil. She has been much improved by continuous treatment.

Case 4.—Male farm-worker. First seen in 1943 at the age of 36. He gave a history that diarrhœa was severe in early childhood and again at the age of 10, but had troubled him little since. His normal bowel habit was to pass two large grey motions daily. He had been off his work for a year before admission to hospital with progressive weakness. His height was 6 ft. 4 in. His voice was high-pitched. He had no axillary or chest hair. Facial hair could not be seen (he shaved once every two months). Pubic hair was sparse. His penis was small and his testes were tiny and soft. The pomum Adami and prostate were both small. He had pellagra-like lesions on the extensor surfaces of both hands and forearms. He had a large ulcer over the right tibia with much surrounding pigmentation. His bones showed osteoporosis and in several bones epiphyseal union had not taken place. His blood-calcium was 8·3 mg. per 100 ml. (varying between 7·5 mg. and 8·5 mg.) and the blood-phosphorus was 3·5 mg. (varying between 3 mg. and 3·6 mg.). Serum-proteins were 6·2 g. per 100 ml. The anæmia was severe, both the peripheral blood and the bone-marrow showing the characteristic picture of a megaloblastic anæmia. The barium meal showed the abnormal small-intestine pattern of the deficiency type. His fat excretion was 19·8 g. in twenty-four hours ≡ 64% of the dried fæces. His 17-ketosteroid excretion (1949, aged 42) was 1·8 mg. in twenty-four hours and the gonadotropin excretion was absent (1950, aged 43). His shy spinsterish personality made him an uncoöperative patient. He was somewhat improved by treatment, but his anæmia was not relieved by any therapy; all the hæmatinics, including folic acid, were used as they became available. He died at home in 1950 and there was no necropsy.

Both these patients suffered from adult cœliac disease, and in both of them there was good reason to believe that the condition had existed since childhood. Although the gonadotropin excretion was not assayed until the woman was 39 years of age and the man 43, it was then absent in both cases. It may be assumed, therefore, that the hypogonadism was secondary to hypopituitarism. The deficient production of gonadotropins in cœliac disease depends on defective absorption of protein; despite a normal intake, these subjects "starve in the midst of plenty." There was no evidence of thyroid or adrenocortical dysfunction (apart from androgen deficiency) in either of these patients.

THE GROWTH HORMONE

Dwarfism is the expected result in cœliac disease which persists into adult life, and short stature was present in case 3. Yet the tall, eunuchoid man (case 4) was still growing in his 30s; this was presumably dependent on the presence of some growth hormone and the almost complete absence of androgens, which had prevented the epiphyseal junctions from closing.

It may be assumed that in him F.S.H. and L.H. were depressed to a greater extent than G.H.

There is no practicable routine assay of the growth hormone in man, and no possibility of its effective clinical assessment. Delay in the appearance of the epiphyseal centres, while it may be associated with depression of the growth hormone, may also depend on several other factors. The position has been still further complicated by the fact that the purified growth hormone does not cause nitrogen retention in man, nor has it yet been shown to cause an enhanced rate of growth in dwarfs suffering from hypopituitarism. The only clinical evidence of a circumstantial sort that a deficiency of the growth hormone can be caused by defective nutrition has been put forward by Talbot et al. (1947).

He and his colleagues found that of 50 children in whom the retardation of growth was sufficient to be called dwarfism, 17 were suffering from emotionally produced anorexia—an anorexia nervosa of childhood. While some of the children resumed normal growth when their appetite returned and their caloric intake was adequate, others failed to make their expected growth increments despite an adequate diet. When some of these children were given methyl-testosterone, normal growth was initiated and the children continued to grow when the testosterone was stopped. Talbot and his colleagues suggested that the malnutrition had caused a deficient production of growth hormone, and the anterior pituitary was stimulated by the testosterone to resume the secretion of the growth hormone.

It appears possible that just as in adult anorexia nervosa the sex hormones can be psychogenically suppressed, so in children the abnormal psychic state may determine a coincident anorexia and inhibition of the growth hormone.

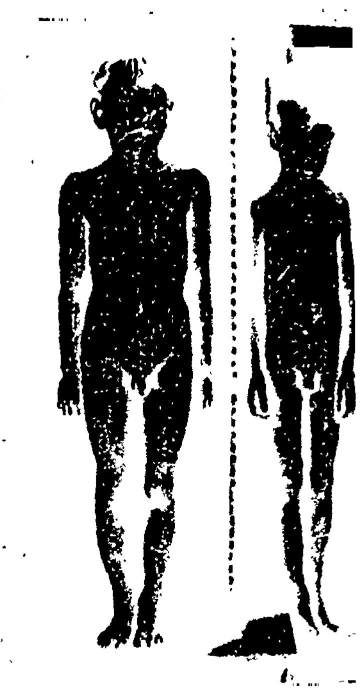
Fig. 4 (case 5)—Anorexia nervosa (righ beside normal boy of same age.

Case 5.—A boy aged 9 years 8 months who has not grown at all in the *last twenty-one months. His height-age is approximately 7–8 years and his bone-age is approximately 6–7 years. The trapezoid is missing from the carpus and there is as yet no distal ulnar epiphysis.* He has no sign of organic *disease; his insulin-sensitivity curve is normal.* He is extremely shy and can be seen in his photograph (fig. 4) trying to hide behind *a tape-measure.* He is unusually tidy and folded his clothes in a neat pile while undressing in my room. He spends three-quarters of an hour in the lavator for fear of soiling himself. His mother, who is the dominatin member of the family, attributes his recent depression an anorexia to envy of a brother who is nearly as tall as himsel although three years younger. While in hospital a year ag his appetite became normal and was adequate for growth It has continued to be so since his discharge, but his depressio has not completely disappeared. Growth has not yet started but I am waiting for two years from the onset of growth failure before using methyl-testosterone in treatment.

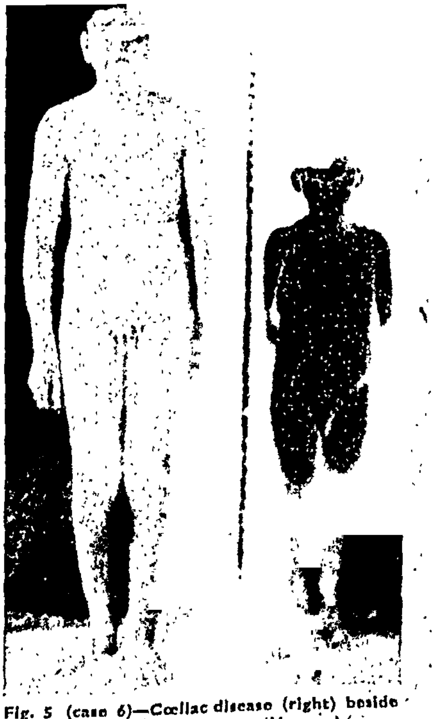
Fig. 5 (case 6)—Cœliac disease (right) beside normal boy of same age (11 years).

A simila failure o growth can be seen in children in uncontrolled cœliac disease.

Case 6.—Now aged 11. He wa first recognised as suffering fro cœliac diseas at the age of 4 He was unde treatment fo three years and was making fai progress but failed to attend the hospital for a year, and at the age of 8 years 10 months was admitted in tetany. His blood-calcium was 6·7 mg. per 100 ml., and his blood-phosphorus 2·5 mg. His serum-proteins were 4·4 g. per 100 ml. (serum-albumin 2·85 g. and serum-globulin 1·55 g.). His height-age and his bone-age were 4 years (40 in. in height and no more than three bones [illegible] the carpus). He made good progress on routine treatment. During his last month in hospital he was given methyl-[illegible] 20 mg. daily, and he grew more than 1 in. in height during this period. Two years later, at the age of 11, his bone-age and his height-age are both approximately 8 years (fig. 5). His general condition is good and his blood chemistry normal. Despite this improvement, his height increments and his bone development are not yet up to average levels. Methyl-testosterone is used intermittently in therapy with excellent effect on serum-proteins, blood-calcium, growth, and epiphyseal development.

SUMMARY

That the production of the growth hormone in man may be depressed by malnutrition, though inherently probable, cannot yet be accepted as proven. That the secretion of the growth hormone may be depressed by emotional factors is possible. That the sex hormones of the anterior pituitary in man can be suppressed both in abnormal psychic states and in malnutrition should be regarded as established. There is no clinical evidence that deficiency of the thyrotropic and adrenocorticotropic hormones occurs either in malnutrition or in depressed states.

Destructive Lesions of the Anterior Pituitary

Sheehan, in a series of brilliant papers, has established the clinical picture of hypopituitarism (Sheehan 1937, 1939, 1940, 1948, 1949 (with Summers), 1950 (with Cooke). His description has been mainly concerned with a postpartum lesion, occurring after obstetric shock and hæmorrhage, which results in an ischæmic necrosis of the pituitary. He cites seventeen signs and symptoms of which the most important are amenorrhœa and gonadal atrophy, loss of pubic and axillary hair, pallor and the absence of skin pigment, increased sensitivity to cold, a low basal metabolic rate, increased insulin-sensitivity, hypoglycæmia, a low urinary excretion of 17-ketosteroids, and a diminished diuresis.

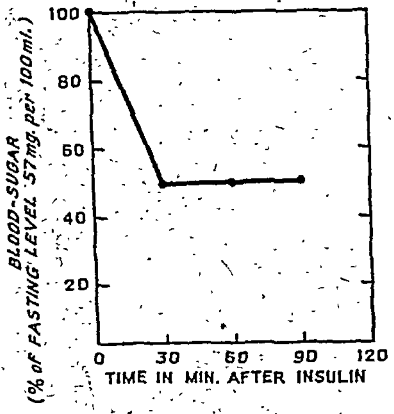

Fig. 6 (case 7)—Sheehan's syndrome. Insulin-sensitivity curve showing hypoglycæmic unresponsiveness.

Sheehan's syndrome is seen in any destructive lesion of the pituitary, whatever its cause; and since the destruction may vary in extent, the appearance and degree of the symptoms will also be variable. Lesions which are partially destructive give an opportunity for studying the degree of deficiency of the various hormones and the onset in time of the clinical manifestations. The 3 cases of anterior pituitary destruction now to be briefly described have been selected from others to display the slow unfolding of the clinical syndrome.

Case 7.—A woman aged 39. Cæsarean section had been performed fourteen years ago after a difficult labour. Bilateral femoral thrombosis followed, and failure of lactation. The pubic hair, which was shaved for the operation, never grew again. The axillary hair disappeared during the following year. Amenorrhœa has been complete. Dyspareunia has occurred but libido was stated to be normal. She complained also of easy fatigability, of sensitivity to cold, and of inertia. Her pallor was striking but anæmia was not marked.

Investigations

Pituitary function.—In the insulin-sensitivity test (in which results are expressed as percentages of the fasting blood-sugar, which was 0·057 mg. per 100 ml.), owing to an error, 4·7 units of insulin (≡ 0·1 unit per kg. body-weight) was given intravenously. Percentage values 100, 55, 55, 55—at half-hourly intervals (fig. 6). Urinary gonadotropins: less than 2 M.U. in twenty-four hours. B.M.R.: −30%. Water-diuresis Kepler A factor ≡ 16 (normal > 30).

Adrenocortical function.—Androgens: 17-ketosteroid excretion 1·3 mg. in twenty-four hours (June 6, 1950); 2·6 mg. (June 16). Electrolyte control: serum-sodium 327 mg. per 100 ml.; serum-potassium 20·5 mg. 11–17-oxysteroids: eosinophil-counts always above 200 per c.mm. Delayed diuresis in the Robinson-Power-Kepler test.

Thyroid function.—B.M.R.: −30%. Blood-cholesterol: 279 mg. per 100 ml. (June 9); 263 mg. (June 24). Electrocardiogram not confirmatory of myxœdema.

Ovarian function.—Atrophic vaginitis. Œstrogens absent from urine. No osteoporosis of skeleton.

Progress

Treatment was with stilbœstrol 2 mg. daily, thyroid gr. 1 twice daily, and methyl-testosterone 10 mg. daily. As the systolic blood-pressure was always over 120 mm., no salt was used in therapy. Well-being improved considerably. She was admitted nine months later for reassessment. Although replacement therapy had been, as expected, partially successful, the only radical change in the results of investigations was that the fasting blood-sugar was higher at 85 mg. per 100 ml. The insulin-sensitivity test was repeated on this occasion with 1·6 units of insulin intravenously, and the result showed that not only had resting hypoglycæmia disappeared but hypoglycæmic responsiveness was now normal. Four hours after 0·3 mg. of adrenaline, a fall in eosinophils from 300 to 200 per c.mm. was observed, and four hours after 25 mg. of A.C.T.H. from 300 to 165 per c.mm. A.C.T.H. 12·5 mg. six-hourly was used for a week in treatment, but although a persistent reduction of eosinophils was observed, there was no increased excretion of urinary 17-ketosteroids (2·2 mg. per 100 ml.). The Kepler factor A improved to 24 after this week's treatment.

This case demonstrates that in partial destruction of the anterior pituitary, although the sexual functions of the pituitary are usually immediately suppressed, with amenorrhœa, failure of lactation, and no growth of sexual hair, yet the clinical expression of the failure of the other tropic hormones is much more gradual and much less absolute. The insulin-resistance mechanism was working so normally that she withstood without discomfort the intravenous injection of 4·7 units of insulin. Fourteen years after the total suppression of androgenic function the adrenal cortex was still supporting in some degree its important functions. Electrolyte control was maintained, insulin resistance was proven, and 11–17-oxysteroid action was not totally absent. Although thyroid function was no doubt to some extent depressed, this patient was not frankly myxœdematous—unlike the next to be described.

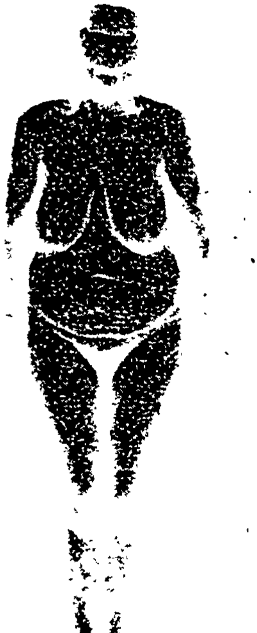

Fig. 7 (case 8)—Sheehan's syndrome.

Case 8.—A woman aged 54 who had a severe postpartum hæmorrhage after the birth of her second child twenty-five years earlier. A gynæcological operation was performed a month later. Her pubic hair has not grown since the operation. (fig. 7). Amenorrhœa has been absolute for twenty-five years. Her axillary hair disappeared in the first year after the confinement. She has been easily fatigued, listless, and sensitive to cold.

These symptoms worsened during the three years before admission. During the preceding three months her voice became hoarse and her appearance was characteristically myxœdematous, but in addition her skin was remarkably white.

Investigations

Pituitary function.—In the insulin-sensitivity test (fig. 8) the fasting blood-sugar was 63 mg. per 100 ml. ≡ 100%. 1·8 units of insulin was administered intravenously and the percentage blood-sugars half an hour, one hour, and one and a half hours later were 63, 58, 63. The patient then became comatose, requiring intravenous glucose one hour and fifty minutes after insulin (blood-sugar 35 mg.). Urinary gonadotropins: less than 3 M.U. in twenty-four hours. B.M.R.: −56%. Water-diuresis Kepler A factor ≡ 8·6 (normal > 30).

Adrenocortical function.—Androgens: 17-ketosteroid excretion 2·4 mg. in twenty-four hours; (repeated) 1·6 mg.; after one week's A.C.T.H. therapy (50 mg. daily) 2·2 mg. Electrolyte control: serum-sodium 282 mg. per 100 ml.; serum-potassium 20·4 mg.; plasma-chlorides 491 mg. 11–17-oxysteroids: eosinophils (several counts), 150, 204, 135, 116 per c.mm.; hourly counts after 25 mg. A.C.T.H., 100, 150, 100, 50. Markedly delayed diuresis in the Robinson-Power-Kepler test was abolished by cortisone and A.C.T.H.

Thyroid function.—B. M. R.: −56 %. Blood-cholesterol (repeated examinations): 356, 312, 339 mg. per 100 ml.

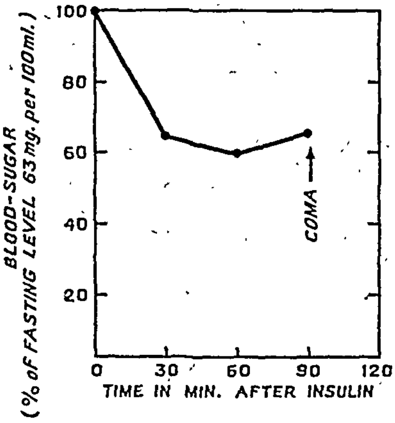

Fig. 8 (case 8)—Sheehan's syndrome. Insulin-sensitivity curve showing hypoglycæmic unresponsiveness. Glucose level remained at 40 mg. per 100 ml., and the patient remained comatose, requiring glucose.

Progress

The adrenocortical failure became acute and 5 g. of salt and 10 ml. of 'Eucortone' was given daily. Serum-sodium increased to 310 mg. per 100 ml. and plasma-chlorides to 573 mg. Eucortone was discontinued, but thyroid and testosterone therapy, with 5 g. salt, was continued daily with much improvement. The insulin-sensitivity test was twice repeated. On March 7, 1951, the percentages were 100, 46, 75, and 84 (fasting blood-sugar 75 mg. per 100 ml.). On March 14, after 25 mg. A.C.T.H. four hours before the test, they were 100, 57, 53, 72, and 77 (fasting blood-sugar 100 mg.).

Although absolute and permanent depression of sexual function had occurred twenty-five years earlier, it was not until a few months before admission that thyroid failure took place and adrenocortical failure threatened. Even then, the eosinophil-counts suggested that 11–17-oxysteroid function was still active, and the adrenal cortex was still capable of stimulation by A.C.T.H. The electrolyte balance was well sustained by only 5 g. of salt daily, and she was able to take gr. 5 of thyroid daily with relief of myxœdema and without further disturbance of adrenocortical function. Later, this patient vomited the salt, and although serum-sodium levels were normal, she was given deoxycortone 3 mg. daily, which proved to be adequate. Her well-being has been further increased by A.C.T.H. therapy. She is now on a maintenance dose of 50 mg. A.C.T.H. weekly and is in good health. No increase of 17-ketosteroids has occurred with therapy. The failure of A.C.T.H. to increase the output of 17-ketosteroids in cases 7 and 8 was noted also by Bartter et al. (1950) in 2 women with panhypopituitarism. They suggested that this might be due to the absence of another pituitary hormone, such as luteinising hormone, which Albright had previously suggested is necessary for the production of adrenal androgens (vide infra).

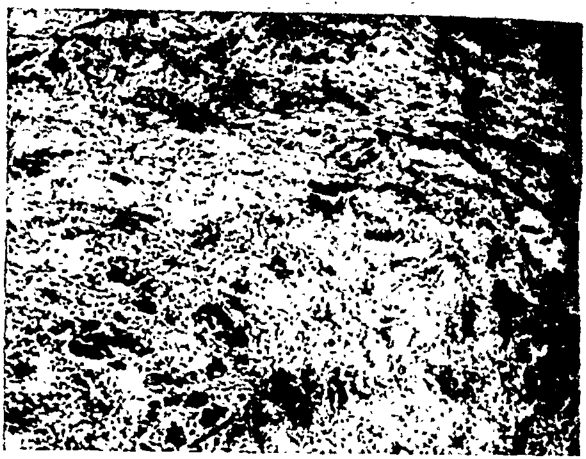

Fig. 9 (case 9)—Simmonds's disease. Section of anterior pituitary (× 112) showing almost complete destruction.

Case 9.—This man was first recognised by me as a pituitary eunuch in 1945 when he was 35. His height was 5 ft. 7 in., his testes were atrophied, he had no axillary hair but sparse pubic hair, and he shaved twice a week. He had lost libido and his skin was very pale. These symptoms had been progressive for the previous five years—i.e., from the age of 30 and ten years before he died. He did not become frankly myxœdematous until 1949, when he came under the care of my colleague Dr. George Kidman. In 1950 he died of pneumonia, and it was found that virtually nothing was left of the anterior pituitary (fig. 9). His thyroid gland was shrunken, with areas of fibrosis, but there was still active thyroid tissue remaining. The testis showed generalised atrophy and the only recognisable layer remaining in the adrenal cortex was the zona glomerulosa which was apparently normal.

The same sequence is shown in this patient. Sexual function ceased completely, but frank myxœdema did not develop until five years after sexual atrophy was established. The zona glomerulosa was still well maintained in the adrenal cortex despite the destruction of the anterior pituitary. There was no clue to the nature of the lesion which destroyed his anterior pituitary.

SUMMARY

A consideration of these cases, and of many other examples in the literature in which the anterior pituitary has been partially destroyed, establishes the principle that as a sequel to the lesion sexual atrophy is usually early and absolute. The menses do not recur, sexual hair fails to grow again if it has been removed, the gonadotropin and the 17-ketosteroid output in the urine fall to negligible levels. Rarely in cases of post-partum necrosis, sexual function persists for a time in a limited degree. Cooke and Sheehan (1950) describe a woman whose menstrual function *continued irregularly* for six years after the pituitary lesion had occurred at the age of 26; she died at 62. By contrast, clinical evidence of thyroid and adrenocortical failure (with *the* exception of the adrenal androgens) unfolds itself slowly and partially.

The Tropic Function of the Anterior Pituitary

It should not be assumed that all the functions of the subsidiary endocrine glands are *totally dependent* on the appropriate tropic hormones from the anterior pituitary. The hypophysectomised animal can, for example, survive without salt therapy, and the *zona glomerulosa* in the adrenal cortex persists after hypophysectomy. Randall and Albert (1951) have recently shown that, after hypophysectomy in rats, the uptake of radio-iodine is about 12% of that in the preoperative animal, and the biological decay of thyroidal I^{131} is reduced to about 13% of the normal rate, proving that both iodine collection and the discharge of thyroxine do occur, though at a much reduced rate. A remnant of 5% of the thyroid gland after subtotal thyroidectomy is stated to prevent the development of clinical myxœdema. Even a limited amount of growth occurs in hypophysectomised animals. Only the sexual function fails utterly.

It is therefore not surprising that in the partially destructive lesions of the anterior pituitary seen in men and women some thyroid function persists and electrolyte control is often well maintained. The remarkable feature of these lesions is that sexual atrophy takes place when the destruction of the anterior lobe has been incomplete.

Sheehan grades the destructive lesions of the adenohypophysis into severe, moderate, minor, and slight. Destruction, he states, is never quite complete: in a moderate lesion, a quarter of the lobe remains, while even in the severe cases between 1% and 20% of the gland remains. The state of the patient does not enable one to assess accurately the degree of anterior pituitary destruction. It is apparent, however, that whenever the damage is severe and even when it may be regarded as moderate, as in case 7 (as judged by the patient's ability fourteen years after the initial lesion to withstand 4·7 units of intravenous insulin and to maintain consciousness despite a persistent blood-sugar of 30 mg. per 100 ml.), the failure of sexual function was immediate and absolute. If it is assumed that both types of secreting cell are diminished in the same proportion, the inference is that a sudden reduction in the gonadotropin secretion, say to 20% of its normal amount, will stop all sexual activity, while thyroid and adrenocortical function are maintained at a reasonable level for many years despite the same quantitative reduction in the tropic hormone. There is evidence—from gonadotropin assay in hypogonadism, from the early onset of amenorrhœa in malnutrition, from the rapid recovery of normal function when nutrition is restored, and from the development of amenorrhœa after comparatively trivial environmental disturbances—that the sexual activities, both primary and secondary, require an optimum secretion of hormones for their normal working; and this may partly explain their early and complete failure in partial destruction of the pituitary. A full explanation of the contrast between partial destruction of the anterior pituitary and complete failure of sexual function must wait upon blood assays of tropic hormones. Biological assays of gonadotropin output and chemical estimation of urinary 17-ketosteroids in hypopituitarism suggest that the failure of production of the sex tropic hormones is more complete than would be expected from a quantitative assessment of the residual pituitary cells. It may be that the remaining secreting cells conserve their reduced total output for the production of A.C.T.H. and T.S.H. which are required to maintain the integrity of the body's economy. In any case, whatever the mechanism, the result is identical with the facts already noted in hypopituitarism due to malnutrition and psychic disorder—the sex-hormone production is easily deranged, while the thyroid and adrenocortical function is tenaciously maintained. Means et al. in 1940 drew attention to the syndrome of "pituitary myxœdema." It follows from what has been written above that myxœdema is not likely to be due to panhypopituitarism in the absence of a concomitant sexual failure. This is a useful diagnostic criterion when pituitary failure is being considered in the ætiology of myxœdema in a patient of reproductive age.

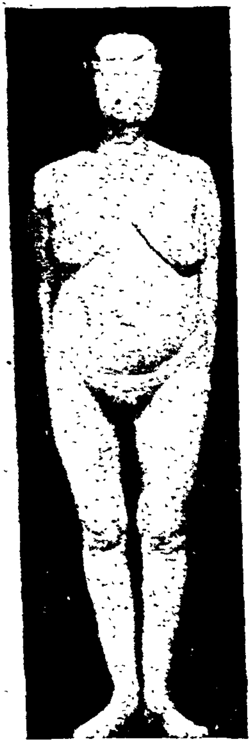

Fig. 10 (case 10)—Chromophobe adenoma. Short stature and amenorrhœa were related to constitutional factors because of the evidence of œstrogen and adrenal androgen activity.

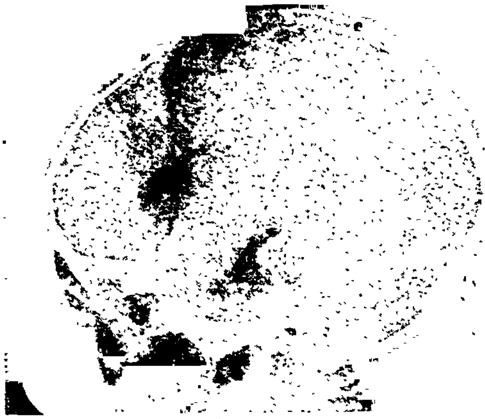

Fig. 11 (case 10)—Radiograph of skull showing almost complete destruction of posterior clinoid processes by the adenoma.

Fuller Albright (1942–43) has for many years advanced cogent arguments that the adrenal androgens are under the control of L.H. from the anterior pituitary acting conjointly with A.C.T.H. A little further support to his view may be drawn from Sheehan's syndrome, in which the sexual hair and the urinary excretion of 17-ketosteroids fail coincidentally with the primary sexual functions.

This observation of the conjoined failure of sexual function and adrenal androgens in women may sometimes be useful in the assessment of pituitary status in destructive lesions:

Case 10.—A woman of 51 came to the hospital complaining of defective vision. She was found by Mr. D. B. H. Dawson to have optic atrophy and bitemporal hemianopia and was referred to me for diagnosis. Her height was 4 ft. 9 in. She had never menstruated. Axillary and pubic hair was within normal limits for her age. The breasts appeared normal but the nipples were small (fig. 10). Insulin-sensitivity and hypoglycæmic responsiveness were normal, and there was no evidence of impaired adrenocortical or thyroid function. Estimation of 17-ketosteroids in the urine varied from 4·3 to 5·6 mg. in twenty-four hours (well within normal limits for her age). Radiography (fig. 11) showed almost complete destruction of the posterior clinoid processes by a large tumour which was later proved at operation to be a chromophobe adenoma. Some osteoporosis of the lumbodorsal spine was also demonstrated.

It must be assumed that both her dwarfism and hypogonadism were not causally related to the pituitary tumour. Her father was short (about 5 ft. 2 in.), and her paternal grandfather shorter still—each had but one child. The normal production and function of adrenal androgens supports the hypothesis that the sex-hormonal cells of the anterior pituitary have not been destroyed by the large tumour.

This linkage of gonadal atrophy and depression of adrenal androgens is seen in other conditions. A patient of mine presenting the characteristic appearance of ovarian agenesis, aged 36, with webbing of the neck and defects of the eye and ear, has absent axillary hair with sparse pubic hair and an output of 17-ketosteroids of 3·6 mg. in twenty-four hours. This association is noted by Turner in a description of his syndrome (1950). A similar genetic association of gonadal atrophy and failure of adrenal androgens in dystrophia myotonica was described by Caughey and Brown (1950). In one female patient of mine suffering from this disorder, the axillary and pubic hair had never developed and the urinary 17-ketosteroids, estimated at the age of 51, were only 1·3 mg. in twenty-four hours. She had, however, borne children and the muscular atrophy did not develop until the age of 48. In another woman, who had also borne children, axillary and pubic hair was present and the urinary 17-ketosteroids were 14·8 mg. in twenty-four hours. Adrenal androgen failure, though a common feature of the disease, is therefore not an invariable manifestation. That the genetic linkage in these two disorders between adrenal and gonadal androgen deficiency depends on a deficient secretion of L.H. is uncertain in the absence of other evidence of pituitary deficiency, but the conjoined failure of gonadal function and of adrenal androgens in postpartum necrosis must be held to support Albright's hypothesis.

The various hypotheses regarding the control of the adrenal cortex by the anterior pituitary and the quantity and nature of the adrenocortical hormones will not be discussed here. They have recently been reviewed by Sayers et al. (1950), who believe that a single tropin (A.C.T.H.) stimulates the adrenal cortex to produce a single steroid or group of steroids. More recent work has established the fact that there are two distinct chemical adrenocorticotropic fractions, though their functions are as yet undefined. Albright's view that L.H. plays a part in the control of adrenal androgens and Greep and Deane's view (1947) that the deoxycortone-like steroids can be secreted autonomously by the zona glomerulosa of the adrenal cortex cannot be denied considerable cogency. They are certainly supported by the consequences of pituitary destruction in man and animals. It should be noted that some of the consequences of destruction of the anterior pituitary which are often attributed to involvement of the thyroid and the adrenal cortex may well be directly, if partially, due to pituitary failure—particularly the low basal metabolic rate and the disturbance in carbohydrate metabolism. The extreme whiteness of the skin which is such a striking feature of Sheehan's syndrome is probably also a direct result of pituitary failure (? melanophore failure in the pars intermedia) and in the cases quoted it was not affected by thyroid, œstrogen, testosterone, or A.C.T.H. therapy.

The Cellular Origin of Pituitary Hormones

The site of production of the various pituitary hormones is still unsettled. As already stated, Albright and Elrick have suggested that all anterior pituitary hormones other than F.S.H. and possibly L.H. take origin from the eosinophil cells. The association of Cushing's syndrome with a basophil adenoma of the pituitary is circumstantial evidence that the basophil cells are also the source of A.C.T.H. There is only one clinical disorder in which a selective interference with the anterior pituitary cells may occur, and that is hæmochromatosis. The following description of a patient provides good evidence that the sexual changes long known to occur in hæmochromatosis depend on the deposit of iron in the basophil cells of the anterior pituitary.

Case 11.—*A man aged 50 who died from hæmochromatosis.* He had been observed for six months before his death, and although the skin biopsy showed melanin but no iron pigment, the diagnosis was easily made by the classical triad of bronzed skin, diabetes, and cirrhosis of the liver. His axillary hair had been diminishing for several years and had disappeared entirely three or four years before admission. His pubic and facial hair was sparse but still present. Libido had diminished over the same period and loss of sexual power had been absolute for three years. His penis was small and his testes soft and very small. The urinary 17-ketosteroid output was recorded as 1·4 mg. in twenty-four hours in May, 1950, 9·2 mg. a fortnight later after methyl-testosterone therapy, and 12·9 mg. three weeks later. The excretion of gonadotropins in two separate specimens was less than 6 M.U. in twenty-four hours. There was no evidence of hypothyroidism. The eosinophils were always below 200 per c.mm., and the Robinson-Power-Kepler test gave a normal result in May, 1950. The following were the serum values for potassium and sodium and the plasma-chlorides in successive months.

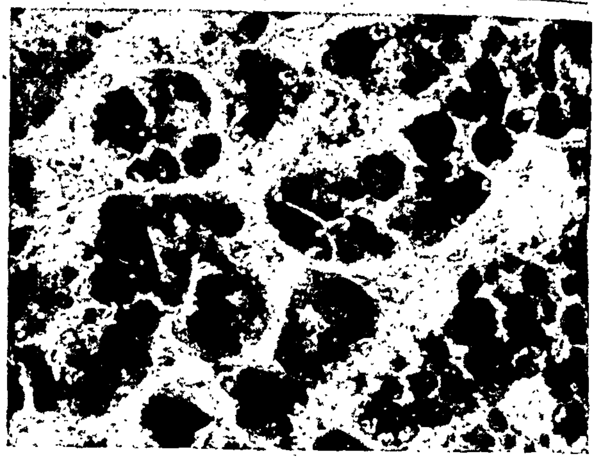
Fig. 12 (case 11)—Hæmochromatosis. Section of pituitary (× 450) showing deposit of iron in the basophil cells and absence of iron in the chromophobe and eosinophil cells.

Electrolyte values in mg. per 100 ml.	May	June	July	August
Serum Na	324	314	318	303
Plasma Cl	562	538	526	468
Serum K	20·1	20·4	25	23

In August he was admitted in heart-failure and he died ten weeks later. Microscopical sections showed that the iron pigment was deposited chiefly in the basophil cells of the anterior pituitary, the chromophobe and eosinophil cells being relatively free of pigment (fig. 12). In the adrenal cortex the iron was deposited in the zona glomerulosa and the zona reticularis had almost disappeared. The zona fasciculata was free of pigment and well preserved. The thyroid gland was normal and the testis showed absence of Leydig cells with degeneration of the tubules.

The evidence in this case seems to establish that the hypogonadism of hæmochromatosis (Sheldon 1935, Kepler et al. 1940) is due to hypopituitarism, and the fact that the iron was mainly deposited in the basophil cells of the anterior lobe indicates that the sex tropic hormones have their origin in these cells. There was no evidence of adrenocortical failure (other than of androgens) until the patient entered the last phase of cardiac failure. Electrolyte control was then disordered, perhaps because of the deposit of iron in the adrenal cortex (mainly in the zona glomerulosa). There was no evidence of hypothyroidism.

These findings uphold the Albright-Elrick hypothesis that only F.S.H. and L.H. are produced by the basophil cells. They can also be used to support the main contention of this paper, that the sex tropic hormones are particularly vulnerable to assault.

The Order of Their Going

Experimental and clinical evidence then agree in demonstrating that whether the depression of anterior pituitary function results from genetic, psychogenic, nutritional, or destructive causes, the sex hormones are almost always involved. The production of the thyroid and adrenocortical hormones (with the exception of the androgens) is much less easily disturbed. Those functions of the endocrine system which are concerned with the integrity of the *milieu intérieur,* and with homœostasis, take precedence over the non-essential functions such as reproduction and growth.

It might be thought that this "order of sacrifice" (to use K. J. Franklin's phrase, 1951) is unbiological, since the future of the race is more important than the survival of the individual. It is apparent that this is not so; for he who emerges from his present state of depression, malnutrition, and diseases may survive both to grow and to reproduce himself another day. Nor should it be assumed that this description of an "order of sacrifice" implies the acceptance of the full doctrine of teleology. The only purpose of living cells is to survive and to reproduce themselves, and to discern a retrospective design in biological phenomena is but to insist that the behaviour of an organism represents the sum of its evolutionary experience. To comprehend a purpose in the response of the body to malnutrition is not to endow the adenohypophysis with mind; for the body's attempts to maintain its integrity in the face of such assaults, both internal and external, are often irrationally extended and to its own hurt. In the endocrine system, and particularly in the pituitary and adrenal glands, these ancient evolutionary processes are today being rapidly revealed by the biochemist and by the clinician.

Summary and Conclusion

1. Cases have been selected to illustrate the course of anterior hypopituitarism. These include examples of genetic deficiency of the pituitary hormones of growth and sex, cases of anorexia nervosa and cœliac disease both in children and adults which show the results of abnormal psychic states and of malnutrition, and examples of Sheehan's syndrome in which partial destruction led to gradual failure of the tropic hormones. A man with hæmochromatosis is described in whom gonadotropin and androgen deficiency was demonstrated for some time before death and the deposit of iron in the pituitary was shown at autopsy to be almost confined to the basophil cells.

2. A sequence of failure of endocrine function is demonstrated in these clinical pictures, and this clinical conclusion can be supported from experimental evidence.

3. Whether the hypopituitarism is the result of malnutrition, of psychological depression, or of destructive disease processes, the sex hormones are always first affected, and with the failure of the sex hormones in destructive lesions goes also the production of adrenal androgens. Clinical evidence of failure of the thyroid gland or of the adrenal cortex may never appear—as in malnutrition or in anorexia nervosa—but it may appear as late as twenty years after the initial failure of the sex hormones, as in postpartum necrosis. This differentiation possibly depends on a quantitative response to the appropriate tropic hormones—more being required to maintain the function of the sex glands and the adrenal androgens. The linkage of the adrenal androgens with the gonads as the first result of anterior pituitary failure may depend on the joint control of adrenal androgens by luteinising hormone (L.H.) together with adrenocorticotropic hormone (A.C.T.H.), as Albright has suggested for other reasons. There is evidence that a minimal degree of electrolyte control (? zona glomerulosa) and of thyroid function can be maintained for long periods even in the absence of pituitary tropic hormones.

4. The production of growth hormone, like that of the sex hormones, may be deranged under similar conditions, but this awaits final proof.

5. It is concluded that the body maintains for as long as possible its homœostatic functions, which procure the stability of the *milieu intérieur* despite malnutrition, abnormal psychic states, and destructive lesions of the anterior pituitary. The less important functions of sex and possibly growth succumb first to any considerable assault. This provides another illustration of what K. J. Franklin has called the "order of sacrifice" in the body's economy.

I am grateful to Dr. A. M. Hain, Dr. A. Jordan, and Dr. C. G. Paine for the endocrine assays, and my thanks are due to my colleague Dr. George Kidman for allowing me to include an account of the necropsy in case 9. Dr. G. R. Osborn and Dr. A. C. Crooke have given me much help with the histological sections.

REFERENCES

Albright, F. (1942–43) *Harvey Lect.* 38, 123.
— Elrick, H. (1948) *Trans. Ass. Amer. Phys.* 61, 42.
Bartter, F. C., Fourman, P., Albright, F., Forbes, A. P., Jefferies, W. M., Griswold, G., Dempsey, E., Bryant, D., Carroll, E. (1950) *J. clin. Invest.* 29, 950.
Bowman, W. E., Reifenstein, E. C. (1950) *In* Progress in Clinical Endocrinology. New York, p. 327.
Caughey, J. E., Brown, J. (1950) *Quart. J. Med.* 19, 303.
Cooke, R. T., Sheehan, H. L. (1950) *Brit. med. J.* i, 928.
D'Angelo, S. A. (1951) *Endocrinology,* 48, 341.
— Paschkis, K. E., Gordon, A. S., Cantarrow, A. (1951) *J. clin. Endocrinol.* 11, 1237.
De Robertis, E. (1948) *Ibid.* 8, 956.
Elliott, T. R. (1914) *Quart. J. Med.* 8, 47.
Evans, H. M., Bishop, K. S. (1923) *J. metab. Res.* 3, 233.
Franklin, K. J. (1951) *Brit. med. J.* 1, 1343.
Fraser, R. (1948) *Proc. R. Soc. Med.* 41, 190.
Gordan, G. S., Bennett, L. L., Li, C. H., Evans, H. M. (1948) *Endocrinology,* 42, 153.
Greep, R. O., Deane, H. W. (1947) *Ibid,* 40, 417.
Hewer, T. F. (1944) *J. Endocrinol.* 3, 397.
Howard, R. P., Sniffen, R. C., Simmons, F. A., Albright, F. (1950) *J. clin. Endocrinol.* 10, 121.
Hubble, D. (1951) *Arch. Dis. Childh.* 26, 130.
Jackson, C. M. (1925) Effects of Inanitation and Malnutrition upon Growth and Structures. Philadelphia.
Jacoby, E. C. (1948) *J. clin. Endocrinol.* 8, 227.
Kepler, E. J., Nichols, D. R., Mills, J. H. (1940) *Ann. intern. Med.* 14, 810.
Li, C. H., Evans, H. M., Simpson, M. E. (1949) *Endocrinology,* 44, 71.
McCullagh, E. P., Tupper, W. R. (1940) *Ann. intern. Med.* 14, 817.
Maddock, W. O., Heller, C. G. (1947) *Proc. Soc. exp. Biol., N.Y.* 66, 595.
Means, J. H., Hertz, S., Lerman, J. (1940) *Trans. Ass. Amer. Phys.* 55, 32.
Randall, R. V., Albert, A. (1951) *Endocrinology,* 48, 327.
Reifenstein, E. C. (1946) *Med. Clin. N. Amer.* 30, 1103.
Samuels, L. T. (1948) Nutrition and Hormones. Amer. Lect. Ser. no. 11. Springfield.
— (1950) *In* Progress in Clinical Endocrinology. New York; p. 511.
Sargant, W. (1951) *Lancet,* ii, 87.
Sayers, G., Cheng, C. P., Samuels, L. T. (1950) *In* Progress in Clinical Endocrinology. New York; p. 513.
Selye, H. (1945) Mont Tremblant Conference.
Sheehan, H. L. (1937) *J. Path. Bact.* 45, 189.
— (1939) *Quart. J. Med.* n.s. 8, 277.
— (1940) *Lancet,* ii, 321.
— (1948) *Proc. R. Soc. Med.* 41, 187.
— Summers, V. K. (1949) *Quart. J. Med.* 18, 319.
Sheldon, J. H [illegible] London.
— (1939) [illegible]
Smith, P. E., [illegible] *nat. Rec.* 50, 85.
Sydenham, A. [illegible] 9.
Talbot, N. B., Sobel, E. H., Bruke, B. S., Lindemann, E., Kaufman, S. B. (1947) *New Engl. J. Med.* 236, 783.
Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Roche, M., Staehelin, D., Wilson, D. L. (1950) *Ibid.* 242, 783.
Turner, H. H. (1950) *In* Progress in Clinical Endocrinology. New York; p. 345.
Young, F. G. (1951) *Brit. med. J.* ii, 1167.

". . . The population of the earth in mid-1950, in round numbers, was 2,400 million . . . the population of the world is likely to increase during the next thirty years by at least 500 million, barring major wars or other unforeseen calamities. If conditions are favourable for population growth, the increase may be by as much as 1,200 million. The total number of people in 1980 would thus be between 2,976 and 3,636 million, and the number per square kilometre of the earth's land area between 22 and 27 instead of 18 as at present. The larger figures would mean an increase of 50 per cent. in approximately one generation, and the smaller an increase of slightly less than 25 per cent. . . . The countries of northern America, north-west-central and southern Europe and Oceania, are likely to contain a shrinking percentage of the world's population during the next thirty years, while those of Latin America, eastern Europe, the Asiatic USSR and Japan are likely to have an increasing share. . . . The demographic trends may therefore tend to worsen the balance in the distribution of peoples and economic opportunities, unless their effect is offset by migration or by more rapid economic development in the regions of greater population growth than in other regions.—*Population Bulletin* of the United Nations; no. 1, December, 1951.

HOSPITAL CROSS-INFECTIONS WITH STAPHYLOCOCCI RESISTANT TO SEVERAL ANTIBIOTICS

SUZANNE K. R. CLARKE
M.B. Brist.
REGISTRAR IN PATHOLOGY

P. G. DALGLEISH
M.D. Lond., M.R.C.P.
MEDICAL REGISTRAR

W. A. GILLESPIE
M.A., M.D. Dubl., M.R.C.P.I., D.P.H.
LECTURER IN CLINICAL PATHOLOGY, UNIVERSITY OF BRISTOL; PATHOLOGIST

ROYAL INFIRMARY, BRISTOL

THE use of antibiotics is being more and more complicated by the emergence and spread of resistant strains of normally sensitive bacteria. The increasing incidence of penicillin-resistant staphylococci in hospitals is the result of cross-infection with a few resistant strains (Barber and Rozwadowska-Dowzenko 1948, Barber et al. 1949, Rountree and Thomson 1949, Cairns and Summers 1950).

We report here the appearance and dissemination, in a hospital, of staphylococci which, in addition to being resistant to penicillin, are also resistant to sulphonamide, streptomycin, chloramphenicol, aureomycin, and terramycin. Besides these organisms, called here "completely resistant," there have appeared staphylococci with what may be called "multiple resistance"—i.e., resistant to several of these drugs, though not all six.

Our attention was directed to this phenomenon by a fatal case of septicæmia from which a completely resistant staphylococcus was isolated after death (see case 1 below). During the next few months several more staphylococci with either complete or multiple resistance were isolated from material sent to the laboratory for routine bacteriological investigation. It was therefore decided to investigate the incidence of resistant staphylococci in selected wards. This was done by taking nasal swabs of patients and staff and by culturing samples of air and dust. The amounts of antibiotics used in the wards were also investigated to see if they were related to the frequency of resistant staphylococci.

The report is concerned only with coagulase-positive staphylococci (*Staphylococcus aureus*), which will be referred to sometimes simply as staphylococci. Chloramphenicol, aureomycin, and terramycin will sometimes be referred to collectively as the newer antibiotics.

METHODS

Wound swabs were cultured on 5% horse-blood nutrient agar. Nasal swabs were cultured similarly and in sodium chloride broth (Maitland and Martyn 1948).

When the direct plate was negative, the salt broth was plated out on blood-agar. The isolation-rate was slightly higher than with direct plating only. Samples of dust from ward furniture were collected on throat swabs and cultured for staphylococci in salt broth only.

Ward air was sampled with settle plates while beds were being made. Each plate was exposed for three hours. Heavy growths, usually including staphylococci, were obtained from the air. On a few occasions, when two or more apparently different colonial varieties of staphylococcus were present on a settle plate, representatives of each were picked for testing. They were counted as distinct strains only if they had different resistance patterns.

The slide coagulase test (Cadness-Graves et al. 1943) was used to check colonies on plates. All cultures were subsequently tested for coagulase by the tube method (Gillespie 1943). Only coagulase-positive staphylococci were included.

Sensitivity Tests

The cultures were tested in batches, with a control organism of known sensitivity in each batch—the Oxford staphylococcus with the antibiotics, and a group-A streptococcus with the sulphonamide tests.

Sulphonamide.—The method of Harper and Cawston (1945) was used with 10 mg. of sulphadiazine per 100 ml. of medium.

Penicillin.—Cultures were heavily streak-inoculated on ditch plates (Fleming 1942), with a concentration of 5 units per ml. in the ditch. The results were clear-cut; resistant cultures grew right across the ditch, whereas sensitive cultures were inhibited to about the same extent as the Oxford staphylococcus.

Streptomycin.—Ditch plates, with 200 µg. per ml., were streak-inoculated. Cultures were either as sensitive as the control or completely resistant.

Aureomycin, chloramphenicol, and terramycin.—The cultures were first tested by a disc method (Fairbrother and Martyn 1951). They were either about as sensitive as the control or were highly resistant (table I). Nearly all the resistant cultures and some of the sensitive cultures were then tested by a serial (doubling) dilution method, with 0·5 ml. of medium per tube. For aureomycin and terramycin the medium was tryptic digest broth (pH 6·8) containing 0·25% glucose (Anderson 1951). Infusion broth (pH 7·2) was used for chloramphenicol. For each the inoculum was one drop (0·02–0·03 ml.) of a 1 in 10 dilution of an overnight infusion broth culture. A control without antibiotic was included with each culture, and an uninoculated broth control with each batch of tests. Readings were made after eighteen hours at 37°C, the minimum inhibiting concentration being the lowest concentration which completely inhibited visible growth. The results agreed completely with the disc method. The cultures were either sensitive or highly resistant (table I). The lack of intermediate values may have been due to the small number of distinct strains, some of which were probably repeated many times in the collection of cultures.

TABLE I—SENSITIVITY RANGES OF THE STAPHYLOCOCCI TO THE NEWER ANTIBIOTICS

How estimated	Aureomycin		Terramycin		Chloramphenicol	
	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant
Disc method :						
No. of cultures tested	199	79	199	79	181	99
Width of zone (mm.) ..	4–8	0–1	4–8	0	5–7	1–2·5
Serial dilution method :						
No. of cultures tested	49	74	49	74	37	88
Minimal inhibiting concentration (µg. per ml.)	0·07–0·6	5–80	0·3–2·5	40–320	2·5–10	40–160

All the cultures were tested by the disc method. A selection were then tested by the serial dilution method.

CLINICAL FINDINGS

During the last quarter of 1951 and the first of 1952 several staphylococci with multiple or complete resistance were isolated from specimens sent to the laboratory for routine bacteriological examination. The sources of the organisms and their resistance patterns are shown in table II. Of the 25 specimens, all from inpatients, 11 were from wounds which had become infected in hospital, 4 were sputa, and 1 was a blood-culture. The 9 urine specimens were from patients who had had suprapubic bladder drainage or prostatectomy. It appeared, therefore, that these staphylococci were causing secondary infections.

In many of the patients the infections were mixed, and it was not possible to decide how much harm was being done by the various organisms. However, there were some in which symptoms were clearly attributable to the staphylococci.

BLE II—STAPHYLOCOCCI (FROM LESIONS OF INPATIENTS) RESISTANT TO ONE OR MORE OF THE NEWER ANTIBIOTICS

Source	No.	Chlor.-R Aureo.-S Terra.-S	Chlor.-S Aureo.-R Terra.-R	Chlor.-R Aureo.-R Terra.-R
ood-culture ..	1	0	0	1
ounds ..	11	2	3	6
rine	9	3	0	6
uta	4	1	2	1
Total.. ..	25	6	5	14

R, Resistant. S, Sensitive.

All these staphylococci were resistant to penicillin, streptomycin, d sulphonamide.

ILLUSTRATIVE CASES

Case 1.—A man, aged 64, was admitted on July 27, 1951, a surgical emergency with a diagnosis of acute cholecystitis. e was treated conservatively with penicillin 1 mega-unit aily and streptomycin 2 g. daily until July 31. The abdominal ndition settled down, but on July 31 he had signs of a est infection and his condition had deteriorated. Chloramphenicol 3 g. daily was given without any improvement his condition till Aug. 2, when aureomycin 2 g. daily was bstituted and continued till Aug. 9. His condition did not nprove, and signs of septicæmia appeared on Aug. 4, when blood-culture grew a *Staph. aureus* reported as resistant penicillin but sensitive to streptomycin, aureomycin, and loramphenicol. On Aug. 7 he was again given chloramphenicol 2 g. daily and this was continued till Aug. 14, when further blood-culture yielded *Staph. aureus* resistant to enicillin and chloramphenicol, and sputum culture gave a rofuse growth of *Staph. aureus* resistant to penicillin, streptoycin, aureomycin, and chloramphenicol. As he was getting orse he was given streptomycin 2 g. daily from Aug. 14 ntil he died on Aug. 20.

Necropsy confirmed the cause of death as staphylococcal epticæmia and bronchopneumonia, but the primary source f infection was not found. The gall-bladder was normal. culture of the tracheal secretion taken at necropsy grew *taph. aureus* which, like the culture from the sputum, was ompletely resistant. Unfortunately the earlier culture had een discarded before the completely resistant staphylooccus was obtained. Therefore it was impossible to decide, rom a comparison of phage patterns and other properties, hether the original strain had altered its resistance or its lace had been taken by a completely resistant strain during reatment.

Case 2.—In October, 1951, a man, aged 32, was struck n the scrotum. The resulting swelling was thought to be hæmatocele. Needle puncture of the swelling was performed n the ward (ward 2—see below); a few ml. of clear fluid was withdrawn but unfortunately not cultured. Two days ater the scrotum showed signs of acute inflammation. rchidectomy was done and revealed a large infected hæmatoele from which a pure growth of completely resistant *Staph. ureus* was obtained. The wound, which was infected with this organism, was slow to heal.

Case 3.—A man, aged 23, developed acute peritonitis after the removal of a gangrenous appendix on Oct. 28, 1951. The operation wound became inflamed. Pus aspirated from it grew *Bact. coli* and *Clostridium* only. The patient was treated with terramycin, which had not previously been used in the hospital, and the peritonitis resolved. His wound, which took four weeks to heal, became secondarily infected with a completely resistant *Staph. aureus*, which for a time was the only organism in the wound.

EVIDENCE OF CROSS-INFECTION

Staphylococci with complete and multiple resistance were isolated from infections in seven different wards, but the majority (including most of the completely resistant cultures) came from two surgical wards—wards 1 and 2. It was therefore decided to study the extent of cross-infection in these wards, each of which measured 102 × 27 × 15 ft. and contained 28 beds. Nasal swabs were taken from patients and staff on several occasions, and dust and air were sampled. In addition, similar sampling was done in ward 3 (28 beds), a recently redecorated surgical ward which was opened in mid-November, 1951, after being closed for several months; and ward 4, a medical ward of 20 beds, in which the use of antibiotics other than penicillin was very small. Also, 40 nasal cultures of *Staph. aureus* were collected in December, 1951, from outpatients attending the casualty department. The results are shown in table III.

Information was obtained about the consumption of antibiotics in the wards under investigation:

Chloramphenicol had been used occasionally from the end of 1949. From February, 1951, more was used, particularly in wards 1 and 2, where up to 4 patients out of 28 were taking chloramphenicol at any one time and 50–100 g. was consumed per month. In ward 3 less than 25 g. was used per month, not more than 1 patient receiving it at a time. In ward 4 chloramphenicol was used only on infrequent occasions.

Aureomycin was used very infrequently from early in 1950 until the beginning of August, 1951. The consumption in wards 1 and 2 then increased considerably, to about 20 g. per month; less than 1 patient on the average received it at a time. In wards 3 and 4 the consumption of aureomycin remained very small: by the end of 1951 only 3 patients in the two wards together had had it since August of that year.

Terramycin was used in the hospital for the first time in November, 1951; up to March, 1952, it had been used only on 3 further occasions.

Penicillin.—The numbers of patients receiving penicillin during 1951 varied from 5 at a time in each of wards 1 and 2 to between 1 and 2 at a time in ward 4. The usual dose was 1 mega-unit daily.

It can be seen from table III that resistance to the newer antibiotics occurred only in staphylococci recovered from ward air and dust as well as from noses of inpatients and staff. Moreover the resistant staphylococci were present in greatest numbers in wards 1 and 2, in which most antibiotic treatment was given.

Resistance to antibiotics other than penicillin was found only in penicillin-resistant staphylococci. The organisms with multiple and complete resistance seem to be variants of the penicillin-resistant strains, which have outnumbered penicillin-sensitive staphylococci in the hospital for some time. In a survey in the hospital made in 1950 (unpublished) it was found that 52% of 89 inpatient nasal staphylococci were penicillin-resistant. This finding was similar to that reported from several

TABLE III—RESISTANCE PATTERNS OF STAPHYLOCOCCI FROM NASAL SWABS, AIR, AND DUST (ISOLATED BETWEEN NOV. 1, 1951, AND FEB. 29, 1952)

—	Penicillin .. .. .. Sulphonamide .. .. Streptomycin .. .. Chloramphenicol .. .. Aureomycin .. .. Terramycin			S S S S S S	R —* —* S S S	R R R R S S	R R R S R R	R R R R R R
Ward or department	Dates	Source	Total staph. isolated					
Wards 1 and 2	Nov. 16 and 28, Jan. 24	114 nasal swabs	75	22	23	11	4	15
	Nov. 16 and 28, Dec. 19, Jan. 28	Air and dust	53	12	8	11	1	21
Ward 3	Feb. 13	29 nasal swabs	18	8	7	0	1	2
	Dec. 15 and Feb. 20	Air and dust	20	3	11	1	3	2
Ward 4	Feb. 13	20 nasal swabs	14	6	7	0	0	1
	Dec. 15 and Feb. 20	Air and dust	19	6	11	0	0	2
Hospital staphylococci total			199	57	67	23	9	43
Casualty dept.	December	Approx. 80 nasal swabs	40	37	3	0	0	0

* In the group of 67 penicillin-resistant staphylococci which were sensitive to the newer antibiotics 31 were resistant to streptomycin and sulphonamide, 16 were resistant to sulphonamide but sensitive to streptomycin, and 20 were sensitive to both.

TABLE IV—PHAGE-TYPES OF RESISTANT STAPHYLOCOCCI IN WARDS 1 AND 2

Resistance pattern	Phage pattern	No. of staphylococci	Source
Complete resistance	53 +	10	Urine (3) Wound (1) Dust (6)
	7/53/54 + and 7/47/47C/53/54 + (these are the same)	3	Nose (1) Dust (2)
Multiple resistance: Sensitive to chloramphenicol only	53 +	1	Nose
Sensitive to aureomycin and terramycin only	53 +	1	Urine
Sensitive to aureomycin, terramycin, and chloramphenicol, resistant to penicillin	53 +	6	Nose
	47C w	1	Nose
	6/7/42B/42E/47/47B/47C/54 +	2	Noses
	52A +	1	Nose
	3A	1	Nose

other hospitals (Barber et al. 1949, Cairns and Summers 1950).

The widespread occurrence of staphylococci with multiple and complete resistance was clearly due to cross-infection. Several of the persons from whom they were recovered had not been treated with antibiotics. The ease with which the organisms were found in dust and air showed that conditions were favourable to airborne spread. Blankets and floors were not oiled.

Some of the cultures from wards 1 and 2 were phage-typed at the Staphylococcus Reference Laboratory, Colindale. The results (table IV) show that one phage pattern (53+) predominated both in the staphylococci which were resistant to the newer antibiotics as well as penicillin and in those which were resistant to penicillin alone. One other different pattern (7/47/53/54+) was also found in both groups. These facts suggest that the completely resistant variants had been selected from at least two distinct penicillin-resistant strains and had spread through the wards. The completely resistant *staphylococcus from case 1 also had the phage pattern* 53+. It is not included in the table, because the patient was in another ward.

DISCUSSION

Probably all staphylococci were originally sensitive to chloramphenicol, aureomycin, and terramycin. In a report on 100 cultures isolated in this country Anderson (1951) found that all were sensitive to aureomycin. Similarly all of the 40 cultures obtained from outpatients in the present study were sensitive to these three antibiotics. It has been found, however, from in-vivo and in-vitro observations, that resistance to aureomycin and terramycin can be acquired fairly readily by staphylococci (Herrell et al. 1950, Pansy et al. 1950, Fusillo and Romansky 1951, Mennier and Schoenbach 1951). The same workers have found that when staphylococci developed resistance to aureomycin, they became resistant to terramycin as well, and vice versa. Unlike coliform bacilli, staphylococci did not exhibit "cross-resistance" between aureomycin or terramycin and chloramphenicol. It seems to be difficult to produce chloramphenicol-resistant staphylococci in vitro, but resistant strains have been found after patients have been treated with chloramphenicol (Altemeier and Culbertson 1951, Pulaski 1951).

The occurrence of "cross-resistance" is a serious disadvantage of the newer antibiotics. It is well illustrated by the resistance to terramycin shown by all the aureomycin-resistant staphylococci in the present study, because terramycin was not used in the hospital until after several of the cultures were isolated.

Finland (1951) has reported an increasing number of staphylococcal infections in the Boston City Hospital. Many of the staphylococci were resistant to aureomycin and terramycin as well as penicillin, but chloramphenicol resistance was uncommon. Combined resistance to antibiotics, similar to that described here, was found by Ransmeier et al. (1951) in a few freshly isolated staphylococci. These workers suggested that sulphonamide may have a place in treating infections with organisms of this sort. However, many of the staphylococci in this hospital are resistant to sulphonamide as well as to the antibiotics.

It is reasonable to suppose that the rate of spread of a drug-resistant staphylococcus by cross-infection in a hospital community will depend partly on the average number of patients who are treated with the drug. If a staphylococcus is resistant to several drugs, all of which are used in the hospital, the selection force in favour of this organism will be correspondingly increased.

Several studies of hospital cross-infection and of the means of combating it have been made (Medical Research Council 1951). Previously one of the most dangerous of cross-infecting organisms was the group-A streptococcus. Since the introduction of sulphonamides and *antibiotics it has been much easier to treat streptococcal infections*. Perhaps partly for this reason many hospitals have not yet applied all the methods of reducing cross-infection which were shown to be of value in the earlier studies. To what extent cross-infection by resistant staphylococci can be reduced by these methods is not known, but it is clear that they should be tried. It is also clear that antibiotics should be used only with good reason; and that when used they should be given *in adequate dosage and for no longer than is really* necessary. The fewer the patients treated with antibiotics the less will be the tendency for cross-infection with resistant organisms to take place.

The dangers which accompany the spread of resistant staphylococci are evident. Serious results of staphylococcal secondary infection of the lung and bowel have occurred during terramycin treatment of pneumonia and urinary infections (Jackson et al. 1951, Womack *et al.* 1952).

SUMMARY

Several infections of hospital inpatients occurred with coagulase-positive staphylococci which were resistant simultaneously to penicillin, sulphonamide, streptomycin, and some or all of the newer antibiotics—aureomycin, terramycin, and chloramphenicol.

The resistant staphylococci were readily recovered from ward air and dust as well as from noses of patients and staff.

The numbers of these organisms recovered from different wards were roughly related to the amounts of antibiotics used in those wards.

Cross-infection is a very important cause of infections by antibiotic-resistant staphylococci in hospital.

We wish to thank Dr. R. E. O. Williams for phage-typing the staphylococci; the consultant staff of the United Bristol Hospitals for permission to study cases under their care; and Prof. C. Bruce Perry for his encouragement and advice. We are indebted to Dr. Gladys L. Hobby, of Chas. Pfizer & Co. Inc., New York, for the terramycin, to Lederle Laboratories Division, Cyanamid Products Ltd., for the aureomycin, and to Parke, Davis & Co. for the chloramphenicol used in the laboratory tests. The terramycin used in treatment was made available by the Medical Research Council.

References at foot of next column

REATMENT OF ACQUIRED HÆMOLYTIC ANÆMIA WITH COMPOUND F ACETATE

M. C. ROSENTHAL
M.D.
ENIOR DAMON RUNYON FELLOW IN HÆMATOLOGY AND INSTRUCTOR IN MEDICINE

T. H. SPAET
M.D.
DAMON RUNYON CLINICAL RESEARCH FELLOW IN HÆMATOLOGY

H. GOLDENBERG
M.D., F.R.C.P. (C)
FELLOW IN HÆMATOLOGY

W. DAMESHEK
M.D., F.A.C.P.
ENIOR PHYSICIAN AND HÆMATOLOGIST, AND PROFESSOR OF CLINICAL MEDICINE

EW ENGLAND CENTER HOSPITAL AND TUFTS COLLEGE MEDICAL SCHOOL, BOSTON, MASS., U.S.A.

From the Ziskind Laboratories of the Hospital and Medical School

THE use of adrenocorticotrophic hormone (A.C.T.H.) and cortisone in the treatment of acquired hæmolytic anæmia associated with circulating antibodies has been attended by striking therapeutic responses (Dameshek et al. 1951, Davidson et al. 1951, Gardner et al. 1951, Unger 1951, Wintrobe et al. 1951). Whether the anæmia is associated with some other disease process ("symptomatic") or is idiopathic in type, it can usually be controlled, provided enough hormone is given. With continued hormone therapy, sustained and at times apparently permanent remissions can be obtained, especially in the idiopathic cases. The demonstration of abnormal antibodies in these cases, in the form of hæmolysins or agglutinins, has been facilitated by immunological techniques such as the use of bovine albumin (Neber and Dameshek 1947), the Coombs test (Loutit and Mollison 1946), and other special tests for hæmolysins (Dacie and De Gruchy 1951). Their use affords the investigator a unique opportunity to follow the effect of various agents on antibody formation in man.

It has previously been noted (Dameshek et al. 1951) that in acquired hæmolytic anæmia the administration of A.C.T.H. or cortisone considerably diminished both circulating and (eventually) fixed antibody. It was then suggested that an actual suppression of antibody formation had taken place—a suggestion supported by the regression of lymphoid tissue which was noted concomitantly in several cases of chronic lymphocytic leukæmia and lymphosarcoma. Recent experimental studies by Bjorneboe et al. (1951), DeVries (1951), and Germuth et al. (1951) seem to confirm these observations. In addition it was found that the diminution of the antibody in a particular case correlated rather well with the potency of the preparation used and the dosage schedule.

Recently published observations (Pincus 1949, Conn 1951) indicate that Compound F (17-hydroxycorticosterone) is the chief substance secreted by the adrenal gland in response to A.C.T.H. administration. Since in Conn's investigations the physiological response to Compound F appeared to be identical with that induced by A.C.T.H., we thought that this hormone should be tried in the treatment of acquired hæmolytic anæmia. It was also hoped that a study of the effect of the hormone on antibody levels and blood constituents in the treated patients would yield useful information as to the best route of administration, the dosage, and the therapeutic effectiveness of Compound F as compared with A.C.T.H. and cortisone.

MATERIALS AND METHODS

The four patients selected showed the classical features of acquired hæmolytic anæmia, including the presence of circulating abnormal antibodies of the hæmagglutinin variety and a positive direct Coombs test. Three were considered to be examples of "symptomatic" hæmolytic anæmia, since in addition to the hæmolytic anæmia each case presented the blood and bone-marrow findings of chronic lymphocytic leukæmia. The fourth patient had no associated demonstrable disease. None had undergone splenectomy. One had had cortisone 100 mg. daily for three months before entering the hospital, with no particular benefit, but the other three had received no therapy.

After base-line studies had been made in each patient, Compound F acetate was administered to two of them in doses of 150 mg. daily intramuscularly (25 mg. every 4 hours): in one of these patients the dosage was doubled for a 6-day period. The other two received Compound F acetate orally, 200 mg. daily being administered in four divided doses. Blood-counts were performed frequently. Fæcal urobilinogen excretion was estimated by the method of Watson (1936), using pooled 4-day specimens. The hæmolytic index was calculated by the method of Miller et al. (1942), and red-cell survival studies were made by the method of Young et al. (1947). Antibody studies included periodic examination of the patient's erythrocytes for the direct Coombs reaction, and titration of the patient's serum for antibody activity, using both saline and 20% bovine albumin as diluents (Neber and Dameshek 1947) and untreated and trypsinised erythrocytes (Rosenthal et al. 1951) as test cells. Search for hæmolysins was made in each case by the trypsin method of Dacie and De Gruchy (1951).

Case-reports

FIRST CASE

A widow, aged 66, was admitted on June 12, 1951, with fatigue and pallor of several months' duration.

History

For at least 5 years she had had a rather benign form of chronic lymphocytic leukæmia, readily controlled by occasional X-ray therapy given over enlarged peripheral lymph nodes. For several years she had had frequent attacks of angina pectoris, with at least two episodes of myocardial infarction. Nitroglycerin and digitalis were necessary.

In May, 1950, she was admitted to the hospital because of severe substernal pain which persisted for 48 hours. No peripheral lymphadenopathy was evident, but the liver and spleen were slightly enlarged, the spleen being felt two fingerbreadths below the costal margin. The red-cell count was 3·2 million per c.mm. and the white-cell count 19,500, with 24% polymorphonuclear leucocytes and 71% lymphocytes (all mature). Because of a reticulocytosis of 4·4–9·6%, a possible hæmolytic process was suspected, and it was found that the serum-bilirubin was 1·4 mg. per 100 ml. (1·3 mg. indirect) and that a direct Coombs test was positive. Search for circulating hæmagglutinins was negative. Although the

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DR. SUZANNE CLARKE AND OTHERS: REFERENCES

Altemeier, W. A., Culbertson, W. R. (1951) *J. Amer. med. Ass.* 145, 449.
Anderson, K. (1951) *J. clin. Path.* 4, 355.
Barber, M., Hayhoe, F. G. J., Whitehead, J. E. M. (1949) *Lancet*, ii, 1120.
— Rozwadowska-Dowzenko, M. (1948) *Ibid*, ii. 641.
Cadness-Graves, B., Williams, R., Harper, G. J., Miles, A. A. (1943) *Ibid*, i, 736.
Cairns, H. J. F., Summers, G. A. C. (1950) *Ibid*, i, 446.
Fairbrother, R. W., Martyn, G. (1951) *J. clin. Path.* 4, 374.
Finland, M. (1951) *Bull. N.Y. Acad. Med.* 27, 199.
Fleming, A. (1942) *Lancet*, i, 732.
Fusillo, M. H., Romansky, M. J. (1951) *Antibiotics*, 1, 107.
Gillespie, E. H. (1943) *Bull. Emerg. publ. Hlth Lab. Serv.* 2, 19.
Harper, G. J., Cawston, W. C. (1945) *J. Path. Bact.* 57, 59.
Herrell, W. E., Heilman, F. R., Wellman, W. E. (1950) *Ann. N.Y. Acad. Sci.* 53, 448.
Jackson, G. G., Haight, T. H., Kass, E. H., Womack, C. R., Gocke, T. M., Finland, M. (1951) *Ann. intern. Med.* 35, 1175.
Maitland, H. B., Martyn, G. (1948) *J. Path. Bact.* 60, 553.
Medical Research Council (1951) Memo. no. 11.
Monnier, J. J., Schoenbach, E. B. (1951) *Antibiotics*, 1, 472.
Pansy, F. E., Khan, P., Pagano, J. F., Donovick, R. (1950) *Proc. Soc. exp. Biol., N.Y.* 75, 618.
Pulaski, E. J. (1951) *J. Amer. med. Ass.* 145, 456.
Ransmeier, J. C., Brown, H. E., Davis, N. (1951) *J. Lab. clin. Med.* 38, 620.
Rountree, P. M., Thomson, E. F. (1949) *Lancet*, ii, 501.
Womack, C. R., Jackson, G. G., Gocke, T. M., Kass, E. H., Haight, T. H., Finland, M. (1952) *Arch. intern. Med.* 89, 240.

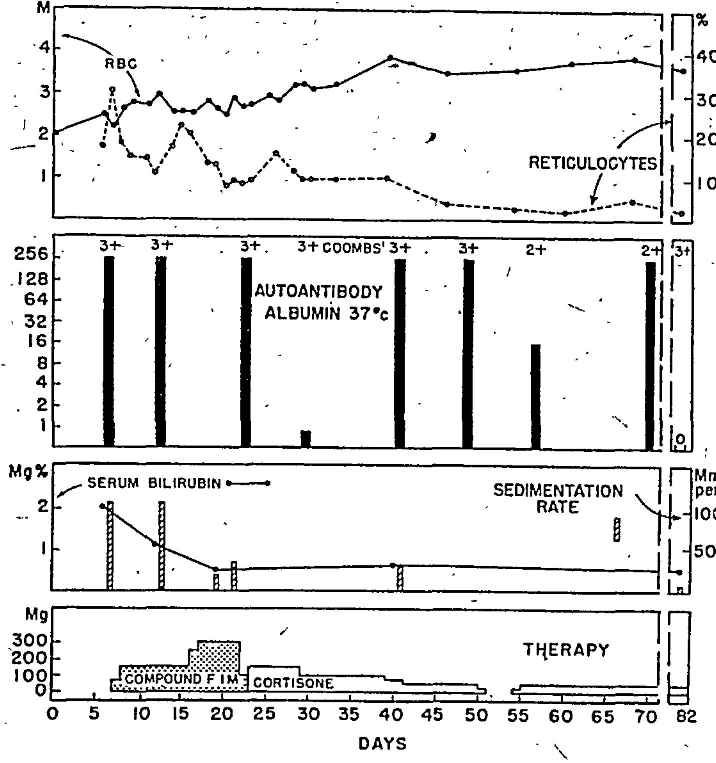

Fig. 1—Hæmatological data of case 1.

patient presented a mild hæmolytic process, this seemed to have ceased by the time of discharge.

During the next year, she had increasing cardiac difficulty and was admitted to another hospital with acute pulmonary œdema. Later, pallor and increasing fatigue developed and she was readmitted to the New England Center Hospital.

Physical Condition

She was pale and slightly icteric. Rather small lymph-nodes were palpated in both axillæ. The spleen was firm and enlarged to three finger-breadths beneath the left costal margin; the liver edge was palpable five finger-breadths beneath the right costal margin, with a smooth non-tender edge. There was no evidence of heart-failure.

Laboratory Findings

The red-cell count was 2·39 million, with hæmoglobin 7·8 g. per 100 ml., hæmatocrit 26%, reticulocytes 16·7%, and platelets 243,700. The white-cell count was 38,300, with 12% polymorphonuclear leucocytes and 82% lymphocytes. Spherocytes as well as polychromatophilic red cells were noted in the peripheral blood smear. There was increased fragility of the red cells to hypotonic saline solutions. The sternal marrow showed marked hypercellularity due to a simultaneous increase in both lymphocytes and normoblasts. The serum-bilirubin level was 2·0 mg. per 100 ml. (1·6 mg. indirect) and the sedimentation-rate (Westergren) was 110 mm. in one hour. The non-protein nitrogen was 41 mg. per 100 ml. and the total cholesterol 135 mg. (70% esters).

An electrocardiogram showed evidence of previous anteroseptal infarction.

A direct Coombs test was strongly positive. An "incomplete" panagglutinin was demonstrated in the patient's serum, most active at 37°C. No hæmolysin could be demonstrated.

Diagnosis

It was evident that the leukæmia was under good control and that the patient was suffering chiefly from acquired hæmolytic anæmia associated with a circulating hæmagglutinin.

Response to Compound F and Cortisone

After a brief period of observation, Compound F acetate 150 mg. was given intramuscularly daily. The patient's course is shown in fig. 1. There were no toxic manifestations, no weight gain, no electrolyte disturbance, and no glycosuria. There was little, if any, euphoria. The red-cell count became stabilised between 2·5 and 2·9 million. The reticulocyte-count fell from 30% to levels of about 10% and then rose to 22%, but there was no appreciable change in the red-cell count. After 8 days' therapy the dosage of Compound F acetate was doubled, but again the red-cell count did not change appreciably. However, the sedimentation-rate fell from 110 to 3 mm. in an hour, the serum-bilirubin level fell from 2·0 to 0·5 mg. per 100 ml.; and the platelets rose from levels of about 250,000 to 550,000, while the white cells increased from about 35,000 to about 110,000, the rise being mainly in lymphocytes. There was no apparent change in the size of the lymph-nodes, spleen, or liver.

After 15 days' therapy with Compound F, cortisone was substituted in a dosage of 150 mg. daily (25 mg. orally every 4 hours). Almost immediately the patient noted a sense of well-being and vigour which she had not had for years. The red-cell count rose gradually, and there was a reticulocytosis of 19%. After 6 days the dosage of cortisone was reduced to 100 mg. daily and then to 50 mg., after which ambulatory home maintenance therapy was instituted. The red-cell count rose eventually to about 4 million with a hæmoglobin of 11 g. per 100 ml., and simultaneously the reticulocytes fell to normal. The leucocyte-count continued to fluctuate between 66,000 to 110,000. The effect of treatment on the amount of antibody in the blood-serum, both with Compound F acetate and cortisone, was difficult to evaluate because of the "coating" of the patient's cells with adsorbed antibody. This resulted in vague end-points when albumin titrations were carried out using the patient's serum against her own red cells. However, after 76 days' therapy the agglutinating antibody in the serum, using bovine albumin, could no longer be demonstrated. A definite diminution in the intensity of the Coombs reaction was noted during cortisone therapy but not with Compound F treatment.

The remission was still being maintained 2 months after initiation of cortisone therapy, and no toxic effects from cortisone were apparent.

SECOND CASE

An estate agent, aged 61, was admitted on May 27, 1951, because of anæmia.

History

In 1948, on routine examination, an elevated white-cell count was discovered and chronic lymphocytic leukæmia was diagnosed. The patient was free from symptoms for three months, but then had increasing fatigue, with a rising white-cell count. Spray X-ray therapy was followed by improvement, but similar therapy in the summer of 1949 gave poor results. In July, 1950, he was admitted to another hospital because of jaundice and anæmia, and from that time fluctuating jaundice and dark urine were noted. Anæmia became quite severe, and he required transfusions at about weekly intervals. Three months before admission to the New England Center Hospital, his physician began the administration of cortisone (100 mg. daily by mouth) but there was no subjective improvement and no decrease in the need for transfusions. Cortisone was discontinued one day before admission.

The patient had had "bronchitis" for 25 years. Although the cough was usually non-productive, in the past few months it had become more severe and there was copious watery sputum.

Physical Condition

He was thin, dyspnœic, pale, and icteric. Breath sounds were diminished at the left base with an audible wheeze throughout both lung fields. The heart was not enlarged. The spleen was felt seven finger-breadths, and the liver four finger-breadths, below the costal margins. No clubbing of the fingers. No lymphadenopathy. Moderate pitting œdema over both pretibial regions.

Laboratory Findings

The red-cell count was 2·75 million, with hæmoglobin 7·6 g. per 100 ml.; hæmatocrit 26%, reticulocytes 30·4%, and platelets 493,250. The white-cell count was 40,100, with 6% polymorphonuclear leucocytes and 89% lymphocytes. The red cells showed moderate to marked spherocytosis and greatly increased polychromatophilia. Several myelocytes were seen. Fragility of red cells was moderately increased. The urinary urobilinogen was 1 : 160, and the fæcal urobilinogen output was 610 mg. per day. Serum-bilirubin was 3·1 mg. per 100 ml. with 2·8 mg. of the indirect variety. The bone-marrow, as in case 1, showed a dual process of lymphocytic infiltration and erythroid hyperplasia. Immunological studies revealed a positive direct Coombs test, and a warm agglutinin active in albumin and against trypsin-treated cells at 37°C. No hæmolysins were found.

Diagnosis

The patient had chronic lymphocytic leukæmia with secondary or "symptomatic" hæmolytic anæmia, but his dyspnœa, cough, and œdema could not be explained solely by these diagnoses. Circulatory dynamics were normal, as was the electrocardiogram. Radiography of the chest revealed collapse of the left lower lung; and this was recent, since previous findings had been essentially negative. It was felt that the peripheral œdema was partly due to the long-continued administration of cortisone. With salt restriction and mercurials, a prompt diuresis occurred.

Response to Compound F and A.C.T.H.

From the 4th hospital day, Compound F acetate was given every 4 hours intramuscularly. Fig. 2 portrays the hæmatological course. There was no improvement in appetite or well-being during the week's trial of Compound F, although the spleen became slightly smaller, the serum-bilirubin level was slightly reduced, and the agglutinin titre fell. Transfusions were not required, but the red-cell count failed to rise, despite an increasing reticulocyte-count. The leucocyte and platelet counts were unchanged.

Administration of A.C.T.H. was begun on the 12th hospital day. Almost at once the patient felt better, except during a brief interval suggestive of withdrawal (Compound F) effects. However, despite a further reticulocytosis the red-cell count did not rise, and although the hæmolytic process seemed to be held in check the patient's condition grew worse.

Terminal Illness

A deep phlebitis of the left leg developed which was treated with heparin and then 'Tromexan'; but therapy with the latter was difficult to stabilise because of fluctuating prothrombin-times. As the patient seemed to recover from this complication, he developed an intermittent cardiac arrhythmia (flutter fibrillation) which could not be controlled with quinidine or digitalis. The association of a collapsed lower lobe of the lung with the refractory cardiac arrhythmia suggested a pulmonary neoplasm, but the patient's poor condition forbade confirmatory investigation. His dyspnœa increased and he died on the 35th hospital day.

Post-mortem Findings

Necropsy revealed, in addition to chronic lymphocytic leukæmia, a widely disseminated bronchogenic carcinoma with pleural and pericardial metastases, as well as thrombophlebitis of the femoral veins with massive pulmonary embolism.

THIRD CASE

A woman of 75 was admitted on June 23, 1951, with pain in the chest and anæmia.

History

Splenomegaly had been discovered in 1947, but she felt well until January, 1950, when she had herpes zoster involving the left lower cervical and upper thoracic nerves. The herpetic eruption disappeared, but she continued to have pain in the left shoulder.

In the latter part of May, 1951, she had an episode of acute congestive heart-failure. This responded partially to digitalis, salt restriction, and mercurial diuretics; but exertional dyspnœa and ankle œdema persisted.

Physical Findings

She was somewhat pale, but there was no clinical icterus, and no lymph-nodes could be felt. The chest was dull to percussion at the base of the left lung, and a few fine crepitant râles were heard at both bases. The heart was slightly enlarged to the left, and a prolonged harsh systolic murmur was heard over the entire precordium and was transmitted to the neck. The liver was extended 6 cm. below the costal margin and the spleen reached the umbilicus. A few scattered petechiæ and small ecchymoses could be seen over the upper limbs, and the lower limbs showed moderate pitting œdema.

Laboratory Findings

The red-cell count was 2·18 million, with hæmoglobin 6·2 g. per 100 ml., and reticulocytes 20%. The white cells numbered 16,400 per c.mm. (21% granulocytes, 74% lymphocytes, 3% monocytes, 1% eosinophils, and 1% myelocytes). A moderate number of spherocytes was seen in the peripheral blood smear. The serum-bilirubin was 1·2 mg. per 100 ml. and the fæcal urobilinogen output was 155 mg. per day. The survival-time of transfused erythrocytes was approximately 8 days. The Coombs test was strongly positive and serum agglutinins of the "incomplete" type were demonstrable. These were active in low dilution against the patient's own cells as well as against normal compatible cells of other persons. The bone-marrow was hypercellular, showing a striking increase in both normoblasts and mature lymphocytes with a paucity of granulocytic elements and megakaryocytes.

The blood non-protein nitrogen was 51 mg. per 100 ml.; the fasting blood-sugar was 88 mg. per 100 ml.; the erythrocyte-sedimentation rate was 124 mm. in one hour (Westergren); and the serum-electrolytes were within normal limits. The cephalin flocculation test was 4+ and the thymol turbidity was 5·1 units. The circulation-time was 14 sec. (arm to tongue) and the venous pressure was 80 mm. of water, with a rise to 130 mm. when pressure was applied to the hepatic region. The electrocardiogram showed T-wave changes consistent with digitalis effects, and radiography of the chest revealed cardiac enlargement, right pleural effusion, and congestive changes in the lung fields.

Reaction to Mercurial Diuretic

On the 6th hospital day the patient was given an injection of the mercurial

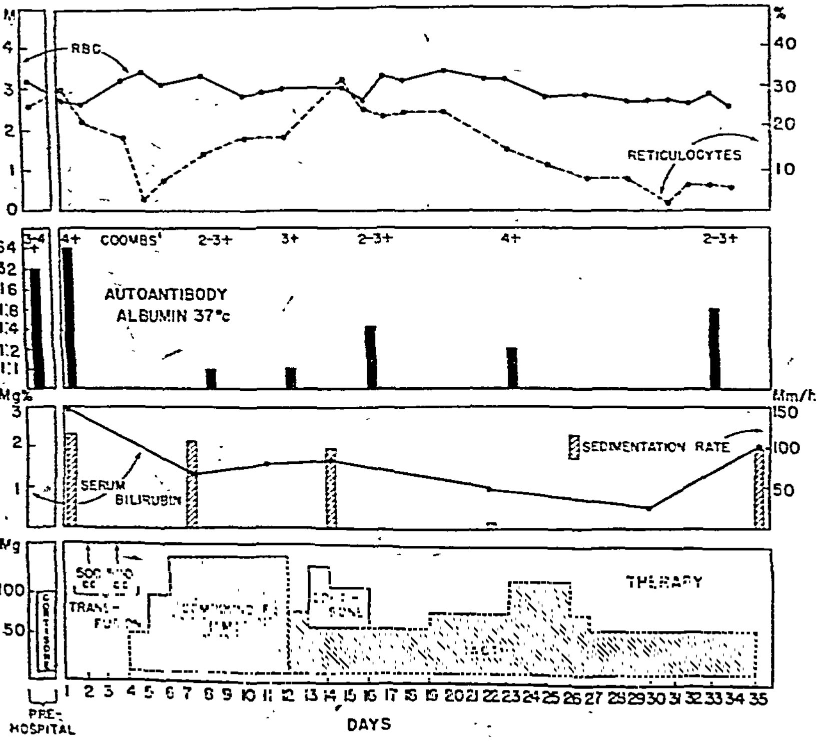

Fig. 2—Hæmatological data of case 2.

diuretic 'Mercuhydrin' because of œdema. This was followed by prostration, a shaking chill, and fever up to 105·2°F. There was no diuresis, but the reaction subsided after 24 hours. A history of previous reactions to this diuretic was then obtained.

Response to Compound F

From the 10th hospital day, Compound F acetate 200 mg. daily was given in four divided doses by mouth in a syrup mixture. The resulting hæmatological changes are shown in fig. 3. After 2 days' therapy the patient said that she was feeling much stronger, though increased appetite and euphoria were not reported. After 7 days' treatment the supply of the drug was exhausted; but it was evident that a remission of the hæmolytic process was under way, as shown by an increase in erythrocytes and hæmoglobin, a decrease in the serum-bilirubin, and a diminution in the titre of agglutinins of the patient's serum against her own erythrocytes.

During the next 5 days without the drug, the red-cell count and hæmoglobin fell sharply and the titre of serum autoagglutinins increased. A second course of Compound F, in the same dosage, began on the 22nd hospital day. As before, a remission of the hæmolytic process was induced and symptoms improved. After a week the hæmolytic index had fallen from 65 to 40 and the red-cell count had risen to 3·24 million.

Last Phase of Illness

During this period the patient had gained about 10 lb. in weight with a big increase in the œdema. She was given a test dose of 0·1 ml. of another mercurial diuretic ('Thiomerin') subcutaneously, which was tolerated without reaction; but on the 30th hospital day, through a nursing error, 1 ml. of mercuhydrin was given intramuscularly. This was followed by a severe reaction with fever up to 103·8°F lasting for about a day. However, she lost 7 lb. in weight through diuresis. On the succeeding 2 days she was given 1 ml. of thiomerin subcutaneously without untoward effect and with an additional diuresis of 8 lb.

At the start of mercurial treatment the serum-electrolytes were within normal limits, but a report of the blood-potassium drawn the day before death showed the level to be 2·4 m.eq. per litre. At this time the serum sodium was 145 m.eq. per litre and the chlorides and carbon dioxide combining-power were within normal limits.

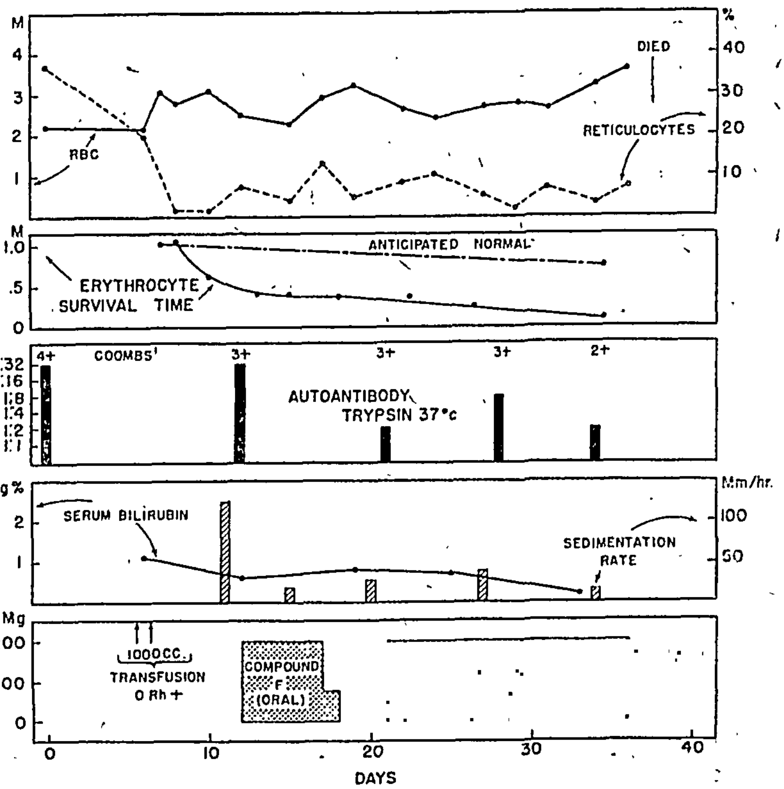

Fig. 3—Hæmatological data of case 3.

On the morning of July 26 the patient was found dead in bed, having had no premonitory symptoms the previous night. Blood-counts on the previous day showed 3·60 million erythrocytes and a hæmoglobin of 10·4 g. per 100 ml. The erythrocyte-sedimentation rate had fallen to 16 mm. in one hour. No change had occurred in the fasting blood-sugar or in the blood-pressure readings while the patient was on Compound F therapy.

Post-mortem Findings

The heart showed narrowing of the coronary vessels, du to arteriosclerotic changes, and areas of focal myocardi fibrosis. There was much pulmonary œdema. The hepat and spleno-megaly were consistent with lymphocytic infiltr tion and the left renal artery was totally occluded. The le kidney was atrophic and the right one showed severe benig nephrosclerosis. Many enlarged retroperitoneal lymph-nod were seen and there was a small dermoid cyst of the rig ovary. Other findings included moderately pronounce œsophageal varices, gall-stones, and generalised seve osteoporosis.

FOURTH CASE

A woman of 70 was admitted on Aug. 30, 1951, wit complaints of fatigue and "a low blood count."

History

Two months before admission she began to feel tired, an her physician noted anæmia. Despite iron and vitamin ca sules her symptoms grew worse, with dyspnœa, palpitatio on exertion, and a rhythmic pounding in the ears at nigh Her complexion became more sallow and her urine was darke than usual. There was no history suggestive of a viral infectio or of any other illness. She had hay-fever each year, and years previously had had a dermatitis which was possibl allergic.

Physical Findings

She was pale and icteric. There was no adenopathy splenic or hepatic enlargement; nor were any other abnorm physical signs found.

Laboratory Findings

The red-cell count was 1·60 million, with hæmoglobi 6·2 g. per 100 ml., hæmatocrit 20%, and reticulocytes 20% The white cells numbered 10,700 per c.mm (66% polymorphonuclear leucocytes, 23% lymphocytes, 5% monocytes, and 6% eosino phils). The platelet-count was 523,20 Marked spherocytosis and polychromatophil macrocytosis were noted on the peripher smear. Urinary urobilinogen was 1:8 The serum-bilirubin was 4·3 mg. per 100 m (3·9 mg. indirect reacting); the blood-ure nitrogen was 12 mg., the blood-sugar 83 mg and the total protein 6·8 g., per 100 m Serum-electrolytes were within normal limit The blood-sedimentation rate was 38 mm. i 1 hour (Westergren). The bone-marrow showe marked erythroid hyperplasia. Both th osmotic fragility test and the mechanic fragility test revealed considerably increase erythrocyte fragility. The direct Coomb test was positive and serum-agglutinins of th "incomplete" type were readily demonstrate against the patient's own cells as well a normal compatible cells. These were mos active at 37°C, less active at 22°C, and leas active at 3°C.

Diagnosis

The patient was evidently suffering from a severe acquired hæmolytic anæmia of an immunological type (auto-sensitisation). N underlying lymphoma or malignancy could b found.

Response to Cortisone F and Cortisone

Because of the patient's advanced years and electrocardiographic evidence of myocardia damage, the severe anæmia was partially corrected by two transfusions of packed cells Then, from the 6th hospital day, she wa given Compound F acetate orally, 200 mg daily in four divided doses. Th

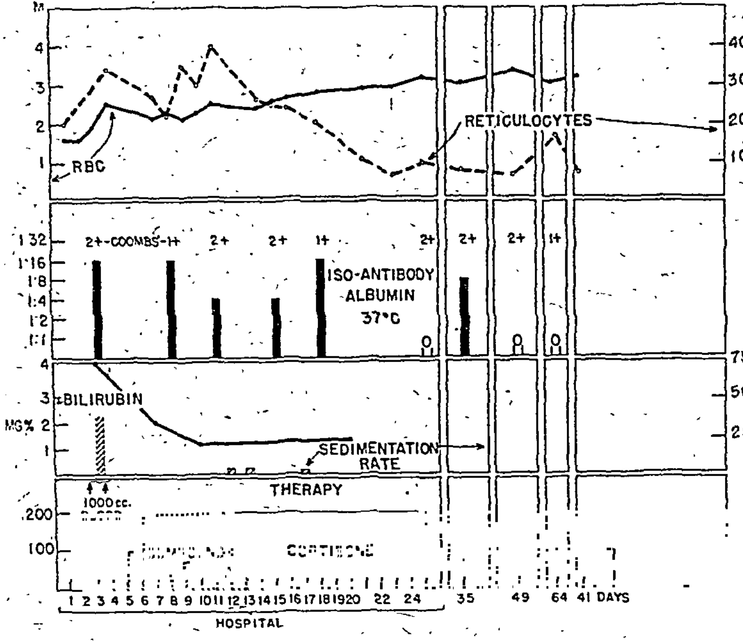

Fig. 4—Hæmatological data of case 4.

æmatological course is shown in fig. 4. Within 2 days, she elt much better—although improved appetite and increased bility to walk—although no undue euphoria was experienced. brisk reticulocytosis up to 40% occurred as well as a leucoytosis of 14,000. Despite the reticulocytosis, the red-cell ount failed to rise, but the trend to increasing anæmia was rrested. The sedimentation-rate fell to 3 mm. in 1 hour and he serum-bilirubin declined to 1·2 mg. per 100 ml. (0·7 mg. ndirect reacting). After a week's treatment the serum-otassium values had fallen from 5·1 m.eq. per litre to ·8 m.eq. Serum-agglutinin values declined only slightly and he Coombs test remained positive.

After 7 days, the Compound F was replaced by cortisone in he same dosage and by the same route. Also potassium chloride g. was given three times daily. On this therapy, the red-cell ount rose to 3·19 million with hæmoglobin 9·3 g. per 100 ml. lthough the Coombs test was still positive, circulating agglu-inins in the sera could no longer be detected, except in a weak itre (1 : 2), by the trypsin technique. The sedimentation-ate remained within normal limits and only low-grade ilirubinæmia persisted (1·4 mg. per 100 ml.).

The patient was discharged from the hospital on Oct. 5 nd advised to take 100 mg. of cortisone daily. Although the ed-cell count and hæmoglobin have been maintained at a onstant level on this dosage, increasing reticulocytosis up to 7% as well as a rising titre of agglutinins suggested that it vas too small. In addition, fluid retention complicated the ituation, because of inadequate salt restriction at home.

Discussion

The demonstration that acquired hæmolytic anæmia associated with circulating antibodies will usually respond dramatically to A.C.T.H. or cortisone has led to drastic revision of therapy in this disease. Whereas previously splenectomy—with its operative risk and therapeutic uncertainty—was almost all we had to offer, medical management is now to be preferred. Both A.C.T.H. and cortisone produce an almost uniform sequence of events in most patients suffering from acquired hæmolytic anæmia associated with auto-antibodies. The patient feels better almost immediately, and the need for transfusions stops abruptly. There is a reticulocytosis with rising red-cell count and longer red-cell survival; the serum-bilirubin level and the fæcal urobilinogen fall, and so (more gradually) does the antibody titre. In some cases (4 of 17 studied) there is even disappearance of the positive direct Coombs reaction.

The present series is admittedly small, but comparison of the effects of Compound F acetate and those of A.C.T.H. or cortisone is illuminating.

In both patients treated with Compound F intramuscularly, the response was only partial. There was no evidence of the psychological "lift" seen with cortisone or A.C.T.H.; and indeed when one of the patients was later treated with A.C.T.H. and the other with cortisone, quick improvement took place. Although the need for transfusions was definitely diminished by Compound F, there was no increase in the red-cell count, despite a transient reticulocytosis up to 22% in one case and up to 18% in the other. In other words, with the intramuscular dosage used, there was simply a "balancing" of the hæmolytic process with red-cell production.

In contrast, both A.C.T.H. and cortisone in comparable dosage in the same patients produced a further reticulocytosis. In one case the red-cell count rose. The other patient, who ultimately proved to have not only chronic lymphocytic leukæmia but also a widely disseminated bronchogenic carcinoma, failed to develop a rise in red-cell count on A.C.T.H. therapy despite reticulocytosis. Both these patients showed a diminution of the serum-bilirubin level, but in only one of the two treated with Compound F intramuscularly was there diminution in the erythrocyte-sedimentation rate. Moreover, this occurred during the period when the patient was receiving 300 mg. of the hormone daily. Interpretation of antibody response was difficult in one patient because of the vague end-point in titrations. This patient (case 1) showed no loss of agglutination activity during administration of Compound F. The titre of antibody fell only after a considerable period of treatment with cortisone, despite a definite and prompt clinical response to this latter agent. The other patient given Compound F intramuscularly (case 2) showed a definite diminution in antibody activity as well as in the strength of the Coombs test, although clinically he was only slightly improved. The effect of the hormone, given intramuscularly, on lymphocytic tissue was variable. One patient showed a slight reduction in the splenomegaly with no significant change in the lymphocytes of the peripheral blood, whereas in the other patient there was a progressively rising lymphocyte-count with no change in the size of the enlarged spleen or liver.

The two patients treated with Compound F intramuscularly did not develop sodium or chloride retention, although both had been extremely susceptible to retention of fluid. One of them showed marked fluid retention with both A.C.T.H. and cortisone, but none with Compound F. Although this might indicate a distinct therapeutic advantage for Compound F, the failure to elicit a complete response in these patients suggested that Compound F was not maximally effective by the intramuscular route, either through poor absorption or through peripheral inactivation. Since this was in agreement with the findings of Conn (1951) with respect to the metabolic ineffectiveness of Compound F acetate by the intramuscular route, the next two patients in the series were treated by Compound F acetate orally. In one of them (case 3) the results were striking, both clinically and hæmatologically. The unexpected death of this patient halted what promised to be a complete remission of the hæmolytic process. Although no comparative studies were made in this case, the response of the hæmolytic process to Compound F acetate given orally seemed to differ in no respect from that achieved with A.C.T.H. or cortisone.

The last patient in this series who received Compound F acetate orally was also treated with identical doses of cortisone. In this patient (case 4), 200 mg. of Compound F daily was only partially successful. Reticulocytosis occurred, as well as leucocytosis, indicating a stimulatory effect on the bone-marrow; but antibody production was not appreciably altered, the net effect being stabilisation of the hæmoglobin and red-cell count. The sedimentation-rate fell to normal, and bilirubinæmia diminished from 4·3 mg. per 100 ml. to 1·2 mg. The patient felt better but had no euphoria. Significantly, hypokalæmia developed on Compound F therapy. When a like dose of cortisone was administered orally, there was a progressive rise in the red-cell count and a decline in the circulating serum hæmagglutinin. On 100 mg. cortisone daily the red-cell count was stabilised, and there was no further rise. Evidence of active hæmolysis was still present on this dosage, suggesting that the amount of hormone needed to suppress the hæmolytic process was higher than is usual. The apparent superiority of cortisone over Compound F in this case may have been due to the relatively brief period of treatment with the latter drug. Some patients with acquired hæmolytic anæmia successfully treated with A.C.T.H. or cortisone alone have not shown dramatic increases in red-cell count until over a week of therapy has elapsed, although earlier cessation of transfusion requirements and a reticulocytosis herald the onset of a remission (Dameshek et al. 1951). Further study is necessary to determine whether Compound F acetate orally has any distinct advantage over Compound E (cortisone) in the treatment of acquired hæmolytic anæmia.

Although these studies were carried out mainly in cases of hæmolytic anæmia superimposed on chronic lymphocytic leukæmia, it is evident from our previous studies that the response to therapy differs in no wise from that in the so-called idiopathic disease. The beneficial response to the various steroid hormones in the hæmolytic anæmia of chronic lymphocytic leukæmia has made the management of this previously very difficult complication relatively easy. It is to be noted that we have observed this complication with increasing frequency in the last 5 years. The development of the hæmolytic state seems to have coincided in some cases with the use of rather large doses of generalised or spray X-ray therapy. In others, however, no cause other than continued rather marked splenomegaly in the presence of a relatively mild leukæmic process has been apparent. It is of interest that therapy with A.C.T.H., cortisone, and Compound F may affect not only the hæmolytic process but also the generalised lymphoid hyperplasia.

Summary

Compound F acetate was administered to four patients with acquired hæmolytic anæmia associated with circulating antibodies. In three cases the hæmolytic process occurred in the course of the more fundamental disease chronic lymphocytic leukæmia, while in the remaining case no associated disease could be established.

Two patients treated with Compound F by the intramuscular route showed a partial response but did not show the usual outspoken remission or the toxic effects seen with intensive A.C.T.H. or cortisone therapy. This difference in effects suggested either poor absorption, poor utilisation, or inactivation of Compound F acetate at the intramuscular site.

Oral therapy with the hormone in one patient resulted in an almost complete remission indistinguishable from that previously achieved in other patients with A.C.T.H. or cortisone; significantly, toxic manifestations in the form of marked fluid retention and hypokalæmia were observed. Similar oral medication in a fourth patient, who had severe idiopathic acquired hæmolytic anæmia, produced only a partial remission. In this patient cortisone given by the same route in the same dosage produced an almost complete remission. In this case Compound F acetate may have been less effective than cortisone.

The value of this new hormone in acquired hæmolytic anæmia requires further study.

The Compound F acetate was supplied for research purposes through the courtesy of Dr. J. M. Carlisle, medical director, Merck & Co. Inc., Rahway, N.J., U.S.A.

REFERENCES

Bjorneboe, M., Fischel, E. E., Stoerk, H. C. (1951) *J. exp. Med.* 93, 37.
Conn, J. W., Louis, L. H., Fajans, S. S. (1951) *Science*, 113, 713.
Dacie, J. C., De Gruchy, G. C. (1951) *J. clin. Path.* 4, 253.
Dameshek, W., Rosenthal, M. C., Schwartz, L. (1951) *New Engl. J. Med.* 244, 117.
Davidson, L. S. P., Duthie, J. H. R., Girdwood, R. H., Sinclair, R. J. G. (1951) *Brit. med. J.* i, 657.
DeVries, J. A. (1951) *J. Immunol.* 65, 1950.
Gardner, F. H., McElfresh, A. E., Harris, J. W., Diamond, L. K. (1951) *J. Lab. clin. Med.* 37, 444.
Germuth, F. G., Oyama, J., Ottinger, B. (1951) *J. exp. Med.* 94, 139.
Loutit, J. F., Mollison, P. L. (1946) *J. Path. Bact.* 58, 711.
Miller, E. B., Singer, K., Dameshek, W. (1942) *Arch. intern. Med.* 70, 727.
Neber, J., Dameshek, W. (1947) *Blood*, 2, 371.
Pincus, G. (1949) From Adrenal Cortex: Transactions of the 1st *Conference, Josiah Macy, Jr., Foundation.* New York; p. 62.
Rosenthal, M. C., Dameshek, W., Burkhardt, R. (1951) *Amer. J. clin. Path.* 21, 635.
Unger, L. J. (1951) *Amer. J. Clin. Path.* 21, 456.
Watson, C. J. (1936) *Ibid*, 6, 458.
Wintrobe, M. M., Cartwright, G. E., Palmer, J. G., Kuhns, W. J., Samuels, L. T. (1951) *Arch. intern. Med.* 88, 310.
Young, L. E., Pfiatzer, R. F., Rafferty, J. A. (1947) *J. Lab. clin. Med.* 32, 489.

WATERHOUSE-FRIDERICHSEN SYNDROME TREATED WITH CORTISONE

REPORT OF TWO CASES

G. E. BREEN
M.D. N.U.I., D.P.H., D.O.M.S.
PHYSICIAN

R. T. D. EMOND
M.B. St. And., D.T.M. & H.
ASSISTANT PHYSICIAN

R. V. WALLEY
M.B. Camb.
REGISTRAR

SOUTH MIDDLESEX HOSPITAL, ISLEWORTH

THE Waterhouse-Friderichsen syndrome is the name commonly applied to fulminating meningococcal infection, characterised in life by collapse and hæmorrhages into the skin and post mortem, in most cases, by hæmorrhage into the adrenal glands. Some would abandon the term because the condition was first described not by Waterhouse (1911) or by Friderichsen (1918) but by Voelcker (1894); and others because it does not comprise certain cases of overwhelming meningeal infection without adrenal hæmorrhage. That the syndrome is to be confined to meningococcal infection has been challenged, pneumococci and streptococci having also been incriminated, but not in recent work, and the consensus of modern opinion regards it as invariably meningococcal in origin. Since the syndrome represents a useful clinicopathological concept, it would seem a pity to discard it.

Clinically it is unique in that no other infection kills so consistently or so quickly. Death sometimes results within twelve, and commonly within twenty-four, hours. The patient, usually a child aged less than 2 years, has often shared in a family "cold," from which he appears to have recovered, when he suddenly becomes restless and fretful and refuses food. There may be vomiting or diarrhœa, a rigor, a convulsion, or rapidly developing delirium. Pronounced cyanosis appears and the respiration-rate often increases. Within a few hours purpura and ecchymoses appear, and collapse rapidly supervenes. It is important to note that there may be no signs of meningitis, whereas the cyanosis and polypnœa may—and often do—strongly suggest pneumonia; hence, unless a lumbar puncture is done, pneumonia may be iagnosed. Even with lumbar puncture the cerebrospinal uid (c.s.f.) may—rarely—show few or equivocal changes nd prove sterile on examination and culture, though the rganisms can usually be recovered from the blood.

Death seems to have been invariable in pre-sulphonmide days, and the first recorded recovery appears to e that reported by Carey (1940). But in spite of antiiotics the case-fatality rate is still frightening; according o Kinsman et al. (1946), in some 200 cases reported up o 1946 there were at most 20 recoveries. This is largely ecause death takes place before the antibiotics have ime to exert their effects. According to Banks and IcCartney (1943) pure "adrenal" cases—i.e., those in vhich the mind is clear—offer a better prognosis than hose in which encephalitis (shown by coma and stertor) nakes an early appearance; none the less we have not een able to trace an instance of recovery in an infant nder the age of 1 year, in whom the condition seems to e especially malignant.

In treatment massive doses of sulphonamides naturally uggest themselves at once. Infusions of glucose, plasma, nd the electrolytes have also been tried to combat the ollapse though, as there is no evidence of hæmoconcenration (Ebert and Stead 1941), they scarcely seem to be ndicated. Various adrenal extracts have also been given —adrenaline and the cortical steroids 'Eucortone,' 'Eschatin,' and deoxycortone, but without notable benefit, though in some cases, especially in adults, they may have helped to prolong life until the antibiotics have had time to act.

Recently, however, Nelson and Goldstein (1951) reported two cases in which cortisone appeared to have proved strikingly effective, abolishing the cyanosis, reversing the fall in blood-pressure, and restoring the secretion of urine, thus clearing the field for chemotherapy. In their first case (that of a boy of 11 years) "within four hours after the initial administration of cortisone a remarkable improvement was witnessed." In the second, a woman aged 28 "began to exhibit a favourable response in a few hours and then improved steadily." Both patients made complete recoveries.

Newman (1951) has also reported a dramatic recovery in a child, aged 4 years, who was almost moribund, and in whom considerable improvement was manifest within twelve hours of the administration of cortisone.

Such a series of recoveries is unprecedented, since in spite of the antibiotics the case-mortality in recent years has remained formidable compared with the enormous reduction in ordinary meningococcal infections. We therefore report the following two cases.

CASE-RECORDS

Case 1.—A girl, aged 2½ years, was admitted late on Jan. 25, 1952, with a history of vomiting and intermittent delirium during the previous night, after which she had been delirious at intervals during the day. When conscious she had complained of headache and backache.

On admission she was deeply cyanosed and extremely restless, flinging her arms and legs about and grinding her teeth. She was unconscious of her surroundings. Her pupils were dilated; the movements of her eyes, face, jaws, and limbs appeared normal. There was very slight neck stiffness, but Kernig's sign was absent. There were numerous purpuric spots on the arms, legs, and lower trunk, with a few large ecchymoses on the legs.

Lumbar puncture (which the child did not appear to feel) produced turbid c.s.f. under increased pressure.

Treatment and Progress.—Sulphadimidine ('Sulphamezathine') 0·75 g. was administered at once intravenously, together with sulphadiazine 0·5 g. by mouth, the latter to be continued four-hourly. Unfortunately a preliminary examination of the c.s.f. brought a confident report that numerous pneumococci were present. This necessitated a hurried revision of the chemotherapy, and aureomycin 0·5 g. four-hourly was substituted for the sulphadiazine.

Next morning (Jan. 26) neck stiffness was more pronounced, further purpuric spots had appeared, the pulse was imperceptible, and the child was conscious for only short intervals. Her eyes were sunken, and she was deeply cyanosed and incontinent of urine. Her heart-rate was 180 and her blood-pressure, which was extremely difficult to measure, was estimated as 88/38 mm. Hg. She had unfortunately vomited the last doses of aureomycin; so intramuscular sulphadimidine 0·5 g. four-hourly and penicillin 500,000 units eight-hourly were substituted.

Shortly after midday a considered report on the c.s.f. was received to the effect that it contained numerous *Neisseria meningitidis* in addition to 2040 cells per c.mm. (all polymorphs), protein 308 mg. per 100 ml., chlorides 670 mg. per 100 ml., and sugar 15 mg. per 100 ml., and gave a positive Pandy test for globulin.

A small supply of cortisone had now been obtained and doses of 25 mg. were given at first six-hourly and later twelve-hourly. Within a few hours the blood-pressure was 95/40 mm. Hg, vomiting had ceased, and no further hæmorrhages were noted. Fluids were taken freely by mouth. Next day (Jan. 27) the temperature had fallen to normal, the pulse had become perceptible, the pulse-rate had dropped to 150, and the blood-pressure had climbed to 105/65. The child's colour was incomparably better, the cyanosis having quite disappeared—she was noted as "flushed and pink"—but she was still restless and incontinent of urine. By the same afternoon she had recovered consciousness and the pulse, the rate of which had now fallen to 120, was of considerably better volume.

Throughout the next day (Jan. 28) the child remained conscious, though she still vomited occasionally. Unfortunately abdominal distension now set in and rapidly became extreme, threatening to embarrass the heart. The pulse-rate, however, remained at 120–140 and the blood-pressure at 104/60 mm. Hg. As it was thought that the distension might be due to loss of muscular tone consequent on potassium excretion as a side-effect of cortisone, a mixture containing potassium was given by mouth and later by stomach-tube. As evening approached, the restlessness, which had considerably diminished, now increased, and during the night of Jan. 28–29 the child had four "fits" characterised by twitching of the right side of the face, the right arm, and the right leg followed by right-sided spasticity, especially of the arm, with an extensor plantar response. On Jan. 29 the condition remained much the same. As no further improvement from cortisone, of which she had now had 200 mg., seemed likely, it was discontinued. The blood-pressure fell slowly to 98/68 mm. Hg, cyanosis reappeared, the eyes became sunken, and the child appeared at times to be unable to swallow. There was fairly frequent vomiting of thick brownish fluid. On Jan. 30 her condition remained unchanged and, as she was now taking little by mouth, an intravenous drip containing 5% glucose was instituted. This was shortly superseded by Darrow's solution. During that day the child's condition continued to deteriorate, and later left-sided twitchings appeared. At 5 A.M. on Jan. 31 she died.

Necropsy Findings (Dr. W. F. Hamilton).—There were a few petechial hæmorrhages on the serous surface of the small intestine; otherwise the alimentary tract was normal. In the anteromedial pole of the left suprarenal gland was a moderate-sized hæmorrhage, and a few minute hæmorrhages were found in the remainder. There was, however, no large-scale destruction of the gland. The right gland showed a few small hæmorrhages.

On the upper and lateral aspect of the surface of the left cerebral hemisphere was a large and rather oval area of hæmorrhage 7×4·5 cm., with its long axis parallel to the long axis of the brain; it was rather posterior than anterior, but its anterior end covered parts of the precentral and post-central gyri. There was hæmorrhage into the underlying cortex, to a depth of about 2–10 mm. In places it was greatest at the junction of the white matter and the grey matter. Surrounding this area were small hæmorrhages affecting the meninges only. There was also one small meningeal hæmorrhage in the right cerebral hemisphere. In the anterior of the brain no hæmorrhages were seen, but the vessels appeared to be dilated. Apart from the hæmorrhagic areas the meninges were not very congested, and no pus was found except a very little in the posterior cerebellar notch. A smear made from this showed a few degenerate pus cells but no organisms.

By a remarkable coincidence the second patient came to the same hospital on the evening of the same day.

Case 2.—A boy, aged 10 months, was admitted on Jan. 31, with a diagnosis of pneumonia and a history of having been taken acutely ill that morning after having had a "cold" for some days.

On admission he was very ill, collapsed, cyanosed, and pyrexial (102°F), with respirations 58 a minute and an uncountable pulse-rate. He was drowsy when left alone but alert when receiving attention. There was a heavy purpuric rash over the legs and lower trunk with a few large ecchymoses, but no evidence of meningitis.

Lumbar puncture produced a cloudy C.S.F under increased pressure and containing 100,000 polymorphs per c.mm., protein 272 mg. per 100 ml., chlorides 706 mg. per 100 ml., and sugar 57 mg. per 100 ml. No organisms were seen, and culture was sterile. Pandy's test for globulin was positive.

Treatment and Progress.—Sulphadimidine 0·5 g. was given intramuscularly and sulphadiazine 0·5 g. by mouth, the latter being continued four-hourly. At the same time treatment with cortisone 25 mg. six-hourly was initiated.

Next morning the temperature had fallen to normal, the cyanosis had disappeared, the pulse was readily perceptible, and the colour was noted as "good." No further purpuric spots had appeared, but some neck stiffness now came on. The heart sounds were strong and regular, and the systolic blood-pressure was (with considerable difficulty) estimated by palpation to be 85 mm. Hg in the posterior tibial artery. The child's general condition was much improved, and in the light of the necropsy findings in case 1 cortisone was discontinued after a total of 75 mg. had been given. By the following morning the child appeared to be almost normal. There was still a hint of neck stiffness, and slight photophobia was now apparent, but he was taking feeds readily and having long peaceful sleeps. Convalescence was uneventful, the purpura and ecchymoses gradually fading except for a large extravasation on the left knee which ulcerated on Feb. 11. He was discharged well on Feb. 19.

DISCUSSION

Although cortisone did not save the life of the first patient, there can be no doubt that it prolonged it for several days and, but for the cerebral hæmorrhages, the child would have recovered. If cortisone had not been given she would probably have died within forty-eight hours of admission.

The important question is when and how these hæmorrhages arose. There are at least five possibilities: (1) they may have begun as part of the original purpuric manifestations; (2) they may have recurred or increased on lumbar puncture, or (3) as a result of the increase in pressure following the administration of cortisone; or (4) they may have resulted from a combination of all the foregoing factors; or (5) they may have been an example of acute focal encephalitis (Banks 1951). From the necropsy findings it was quite impossible to say which of these hypotheses was correct. From the clinical point of view, however, it seemed almost certain that the bleedings coincided with the "fits" noted on the night of Jan. 28–29. Cortisone not uncommonly produces a slight rise of blood-pressure in normotensive patients—but only after some ten to fourteen days' therapy: whether it increases or decreases the clotting-time is not very clear. Similar focal hæmorrhages are by no means unknown in the ordinary forms of purulent meningitis, often occurring when the meningitis has cleared (Banks 1951). At all events it would not be unfair to regard it as a hazard, rare but normal, of the meningitis, and unrelated to the cortisone therapy.

Case 2 can be regarded as entirely supporting the finding of Nelson and Goldstein (1951). The child admittedly came under treatment within twelve hours, but even so the improvement was remarkable and, compared with what is normally to be expected, the contrast was overwhelming. We have not been able to find an instance of recovery at such an age, or any such prompt recovery at any age. As many patients have been treated quite as intensively by chemotherapy, it seems impossible to deny cortisone the credit for the result. The small amount required suggests that irreversible adrenal damage is not always necessarily present in these cases, but that temporary adrenal exhaustion can produce the clinical picture.

SUMMARY

Two cases of the Waterhouse-Friderichsen syndrome are described. Both were treated, in addition to chemotherapy, with cortisone 25 mg. six-hourly.

The first patient, who was in extremis before treatment was begun, considerably improved, only to succumb to massive cerebral hæmorrhage five days later. The second, which came under treatment about twelve hours after the onset, made a complete and uninterrupted recovery.

It is concluded that cortisone is of great value in the treatment of this syndrome.

We wish to thank Dr. R. A. J. Asher, of the Central Middlesex Hospital, for supplying us with the cortisone.

REFERENCES

Banks, H. S. (1951) Modern Practice in Infectious Fevers. London vol. I, p. 313.
— McCartney, J. E. (1943) *Lancet*, i, 771.
Carey, T. N. (1940) *Ann. intern. Med.* 13, 1740.
Ebert, R. V., Stead, E. A. jun. (1941) *J. clin. Invest.* 20, 671.
Friderichsen, C. (1918) *Jb. Kinderheilk.* 87, 109.
Kinsman, J., D'Alonzo, C. A., Russi, S. (1946), *Arch. intern. Med.* 78, 139.
Nelson, J., Goldstein, N. (1951) *J. Amer. med. Ass.* 146, 1193.
Newman, L. R. (1951) *Ibid*, p. 1229.
Voelcker, R. (1894) *Middlesex Hosp. Rep. Reg.*
Waterhouse, R. (1911) *Lancet*, i, 577.

SLIPPING RIB IN A NEWBORN CHILD

MALCOLM ARTHURTON
M.B. Lond., M.R.C.P., D.C.H.
SENIOR MEDICAL REGISTRAR, WESTMINSTER CHILDREN'S HOSPITAL; LATE REGISTRAR, INSTITUTE OF CHILD HEALTH, POSTGRADUATE MEDICAL SCHOOL OF LONDON

THE term slipping rib was first used by Davies-Colley (1922) when describing two cases of displacement of the tenth costal cartilage. Harrison (1901), however, seems to have been the first to observe the condition but refers only briefly to his patient. Before 1922 Clarke (1908) and Cyriax (1919) were the only other observers who published details of their findings.

The subject and literature of slipping rib cartilage were fully reviewed by Holmes (1941), whose own records include details of the youngest recorded example of the condition, in a boy aged 6 years. More recently Stevenson (1951) has described 5 more cases of the same condition under the title of nerve nipping at the intercostal margin.

No report has been published of the occurrence of slipping rib during the neonatal period; so the following case is of interest.

CASE-RECORD

The patient, a full-term male infant weighing 5 lb., was delivered by lower-segment cæsarean section. There had been no signs of fœtal distress. Owing to the persistence of cyanosis associated with inspiratory recession of the lower ribs, the infant was placed in an oxygen tent, where his colour became normal.

Examination ten hours after birth revealed a premature looking baby who became cyanosed when removed from the oxygen tent. The respirations were regular at 64 per minute, mainly abdominal, and accompanied by an expiratory grunt. Pronounced inspiratory recession of the lower ribs and lower sternum was present. There was no subcutaneous emphysema. A diffuse but distinct shock was most easily palpable over the sixth right rib, $1^{1}/_{4}$ in. from the midline, just before the completion of inspiration. At the same phase of respiration a diffuse and loud snapping sound was most clearly heard on auscultation at the same site. Air entry was poor in all areas of the chest, but no adventitious sounds were heard. The heart sounds were normal.

Severe atelectasis was diagnosed. Oxygen therapy was continued, and systemic penicillin was prescribed for three days as prophylaxis against possible pulmonary infection.

On the second day of life the baby's general condition remained unchanged, but the shock and snap were now also noted during expiration. Radiography of the chest at this stage revealed no evidence of a fractured rib, pneumothorax, mediastinal emphysema, or congenital abnormality of the thoracic bony cage.

At the age of three days there was clinical improvement, rib recession being less except when the child cried; then the snapping sound was audible at the cot side without the aid of a stethoscope.

Five days after birth there was no palpable or audible abnormality in the chest, but the snapping sound was reproduced when deliberate obstruction of the nose forced the child to make excessive efforts at inspiration. On the eighth day rib recession was no longer seen.

The baby, weighing 5 lb. 12½ oz., was discharged home, fully breast-fed at the age of 21 days. When he was seen a month later, no abnormalities were noted on clinical examination of the chest. A more recent examination, at the age of 18 months, revealed a very healthy infant whose chest, including thoracic cage, was normal.

Before discharge, fluoroscopy with the aid of a marker had shown in the lateral view that the unusual shock and sound appeared to arise at the level of the anterior costal origin of the diaphragm on the right side.

DISCUSSION

Slipping rib is caused by indirect violence more often than by direct injury (Holmes 1941). The severe muscular effort involved in lifting, pushing, twisting, flexion, and extension of the trunk, childbirth, or severe coughing—e.g., in whooping-cough—may cause or aggravate the condition.

The unusual findings on palpation and auscultation in the present case seem to be due to the recession of the lower ribs and consequent overriding of the sixth and seventh, or seventh and eighth, costal cartilages as a result of severe atelectasis. Owing to the size of the patient and the diffuse nature of the sound and shock, it was impossible to be certain which of these ribs were affected. Since the seventh costal cartilage articulates with the sternum, the second of these possibilities was considered the more likely. This idea is supported by the gradual disappearance of the abnormal signs with the advent of normal respiratory movements and by the radiological findings.

Holmes (1941) emphasises that slipping rib cartilage, with few exceptions, affects the eighth, ninth, and tenth, or vertebrochondral, ribs, involving the distal ends of the anterior rib cartilages, their interchondral articulations, and the intercostal nerves. Ballon and Spector (1938) make it clear, however, that a similar clinical picture may result from a fracture of a costal cartilage or a dislocation at either the costochondral junctions or the chondrosternal joints. These workers and others (Marshall 1922, Bisgård 1931, Graham et al. 1935) do in fact include examples of the last two conditions among their case-records of slipping rib. There was no evidence, however, that such ætiological factors were responsible for the unusual signs in the present case.

I wish to thank Prof. Alan Moncrieff for permission to publish this case.

REFERENCES

Ballon, H. C., Spector, L. (1938) *Canad. med. Ass. J.* 39, 355.
Bisgard, J. D. (1931) *J. Amer. med. Ass.* 97, 23.
Clarke, J. J. (1908) *Brit. med. J.* ii, 1135.
Cyriax, E. F. (1919) *Practitioner*, 102, 314.
Davies-Colley, R. (1922) *Brit. med. J.* i, 432.
Graham, E. A., Singer, J. J., Ballon, H. C. (1935) Surgical Diseases of the Chest. Philadelphia.
Harrison, S. G. (1901) *Brit. med. J.* ii, 78.
Holmes, J. F. (1941) *Amer. J. Surg.* 54, 326.
Marshall, C. J. (1922) *Brit. med. J.* i, 516.
Stevenson, F. H. (1951) *Lancet*, ii, 969.

Preliminary Communications

CORTISONE AND EXPERIMENTAL EXOPHTHALMOS

THE demonstration that connective-tissue changes are one of the factors leading to ocular protrusion,[1–3] the well-known effect of cortisone on such tissue, and the realisation that most workers had used impure pituitary extracts to produce exophthalmos prompted the following series of experiments. Some preliminary results have already been reported.[4]

25 immature male and female guineapigs, weighing about 200 g. each, were given daily intraperitoneal injections of thyrotropin, the thyroid-stimulating hormone (T.S.H.) (Parke, Davis), 3 mg. in 0·5 ml. of saline, either with or without cortisone ('Cortone') (Merck) 12·5 mg. intramuscularly. The resulting proptosis was assessed by a modification of Pochin's method[5] of measuring the intercorneal distance. Whereas T.S.H. alone produced moderate or no exophthalmos, the simultaneous administration of cortisone considerably intensified the proptosis. The difference obtained was statistically significant. This action could be verified by injecting cortisone late in the course of an experiment to animals in which T.S.H. alone had failed to produce ocular protrusion. It was unchanged by giving an excess of ascorbic acid, but it could be reduced by giving thyroxine. In the intact animal the initial high degree of proptosis could not be maintained throughout the experimental thyrotoxicosis. Adrenocorticotropic hormone (A.C.T.H.) (Ciba) was given to 3 animals, and it also increased the experimental T.S.H. exophthalmos. The results are summarised in the accompanying table.

INCREASE IN INTERCORNEAL DISTANCE (I.C.D.) IN GUINEAPIGS HAVING THYROTROPIN (T.S.H.) ALONE OR WITH CORTISONE OR A.C.T.H.

Treatment	No. of animals								
	Increase in I.C.D. (in.)					% increase in I.C.D.			
	0–0·02	0·02–0·04	0·04–0·06	0·06–0·08	Over 0·08	0–2	2–4	4–6	Over 6
T.S.H. only	6	7	5	1	..	7	7	4	1
T.S.H. and cortisone	..	2	2	2	5	..	2	3	6
T.S.H. and A.C.T.H.	..	..	1	..	2	..	..	1	2

Essentially the same conclusions were reached when the experiment was repeated on 10 thyroidectomised guineapigs. Whereas the average ocular protrusion in animals receiving T.S.H. alone ranged from 0·032 to 0·054 in., it varied in the cortisone group from 0·065 to 0·090 in. The difference was again statistically significant. The proptosis could be rapidly reversed despite continued treatment with cortisone and T.S.H. if thyroxine was given as well. This is probably another manifestation of the antagonism between the thyroid and the adrenal hormones, and explains why the initial high degree of proptosis in the intact group could not be maintained.

As the intensifying effect of cortisone on T.S.H.-induced exophthalmos occurred in thyroidectomised as well as in intact animals, it cannot be accounted for by a depression of thyroid activity by cortisone. It may be

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1. Smelser, G. K. *Amer. J. Path.* 1939, 15, 341.
2. Ludwig, A. W., Boas, N. F., Soffer, L. J. *Proc. Soc. exp. Biol., N.Y.* 1950, 73, 137.
3. Asboe-Hansen, G., Iverson, K. *Acta endocrinol.* 1951, 8, 90.
4. Aterman, K. *Brit. med. J.* 1951, ii, 609; *Proc. R. Soc. Med.* 1952, 45, 241.
5. Pochin, E. E. *Clin. Sci.* 1944, 5, 75.

that cortisone acts directly on the connective tissues of the body and that the proptosis is only the most prominent sign of a generalised process. The beneficial effect of thyroxine, used in the treatment of some patients with exophthalmos, cannot be due to the inhibition of T.S.H. production in the pituitary as is commonly postulated, but it could be explained as the result of a raised basal metabolic rate leading to rapid and increased utilisation of the excess adrenal steroids.

The details of this work and its clinical implications will be published later.

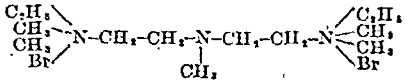
Department of Anatomy,
University of Birmingham

K. ATERMAN
M.D. Prague, M.R.C.P., D.C.H.

A NEW GANGLION-BLOCKING AGENT

TRIAL OF 'CIBA 9295' IN MAN

IN animal experiments the new compound, N,N,N',N'-3-pentamethyl-N,N'-diethyl-3-aza-pentane-1, 5-diammonium-dibromide has shown great potency as a ganglion-blocking agent.[1] Its structural formula is:



$$\begin{matrix}C_2H_5\diagdown & & & & & & \diagup C_2H_5\\ CH_3-N & -CH_2-CH_2- & N & -CH_2-CH_2- & & N & \!\!<^{CH_3}_{CH_3}\\ CH_3\ \ \ Br\diagup & & | & & & & \diagdown Br\\ & & CH_3 & & & & \end{matrix}$$

This diquaternary ammonium dibromide is highly soluble in water and is neutral in aqueous solution (pH = approx. 6·5). It resembles the pentamethylene bistrimethylammonium dihalides[2] more than the bistriethyl ammonium salts described by Chou and De Elio.[3] Consequently, it might be expected to be a powerful ganglion-blocking agent, devoid of the stimulating actions of muscarine or nicotine. Unless the interposition of a nitrogen atom renders invalid the analogy with the methonium compounds, this *new compound* has a polymethylene chain of optimal length for ganglion-blocking activity.

Animal experiments[1] have in fact shown it to be twice as potent a blocking agent as tetraethylammonium bromide, with a longer action. It was found to antagonise the excitatory effect of nicotine and to block afferent sympathetic impulses and it was equally well tolerated on repeated administration. The lethal doses by oral, subcutaneous, and intravenous routes were approximately twice those of tetraethylammonium bromide; death was due to respiratory failure and paralysis resembling that caused by curare. The drug has been shown to increase the pressor effect of injected adrenaline, but its general effect in animals was to reduce blood-pressure and to increase blood-flow to various organs. The coronary flow was increased with doses of less than 3 mg. per kg. body-weight, but with larger doses it decreased, probably because of the fall of blood-pressure.

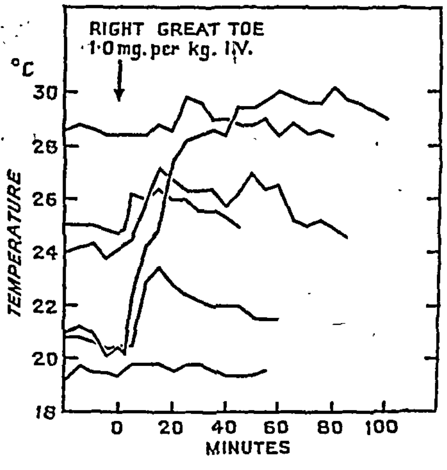


Fig. 1—Skin-temperatures of right great toe in six patients given 1 mg. per kg. of body-weight.

We gave the preparation intravenously to normal adult male volunteers, all of whom were patients awaiting operation in general surgical wards. The experiments were conducted in a quiet room maintained at an equable temperature. None of the subjects had eaten for two hours before the experiment and no food was permitted during its course. With all four limbs exposed, the patients lay quietly for a preliminary period of at least thirty minutes, to allow them to become accustomed to their new surroundings. The following observations were then made every five minutes:

1. Skin-temperatures of great toes, thumbs, and calves using a 'Light' skin thermometer with multiple fixed electrodes.
2. Oscillometric readings of one calf.
3. Pulse-rate.
4. Blood-pressure.

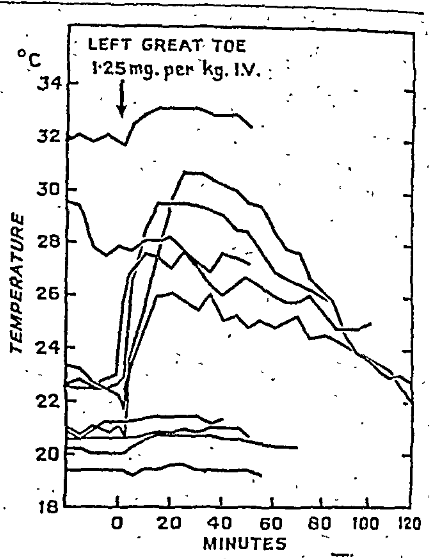


Fig. 2—Skin-temperatures of left great toe in ten patients given 1·25 mg. per kg. of body-weight.

When a satisfactory series of base-line observations had been obtained the drug was injected. (If, after ninety minutes, a satisfactory base-line had not been obtained, the experiment was abandoned.) Readings were taken within two minutes of the injection and were repeated every five minutes. The patients were questioned about their sensations; the presence or absence of flushing, sweating, pallor, or changes in the size of pupils was noted and tests for paralysis of accommodation were carried out. At the end of each experiment blood-pressure readings were taken with the patient standing.

The drug was given to 26 patients on 30 occasions, the dose being gradually increased from 0·3 mg. per kg. body-weight. No definite response was obtained with less than 1·0 mg. per kg.; but with doses of 1 mg., 1·25 mg., and 1·5 mg. per kg. a definite response was obtained on 18 of 22 occasions. The changes in skin-temperature of great toes and in blood-pressure are illustrated in figs. 1–4. The skin-temperatures of the calves showed only insignificant changes, and the skin-temperature of the thumbs usually followed those of the toes, although the change was less—as was to be expected because of the invariably higher initial thumb-temperatures. In 1 subject there was a rise of upper-limb skin-temperatures of 5°C without change in the lower limbs. The 2 instances in which the greatest increases in lower-limb temperatures

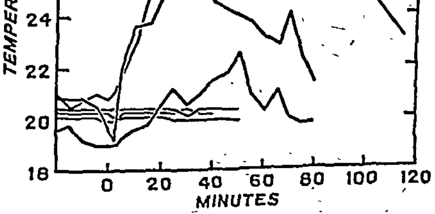


Fig. 3—Skin-temperatures of left great toe in six patients given 1·5 mg. per kg. of body-weight.

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1. Bein, H. G., Meier, R. *Experientia*, 1950, 6, 351.
2. Paton, W. D. M., Zaimis, E. J. *Brit. J. Pharmacol.* 1949, 4, 381.
3. Chou, T. C., De Elio, F. J. *Ibid*, 1947, 2, 268.

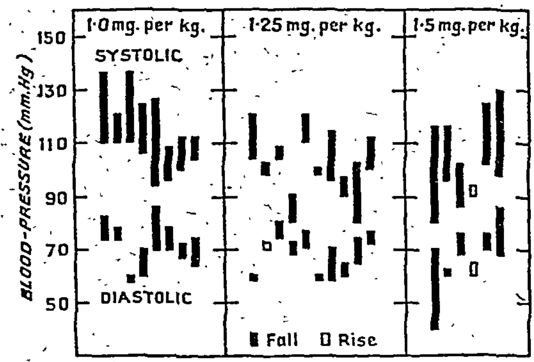

Fig. 4—Greatest changes in blood-pressure in twenty-four patients after intravenous injection.

re noted showed exceptional changes in the upper nbs. In 1 of these cases the thumb-temperatures fell 4°C; in the other it rose by 2°C immediately after jection and thereafter fell steadily. Skin-temperature anges reached a maximum within twenty to sixty inutes of injection and were usually still above se-line values at the end of two hours.

Blood-pressures almost always fell on administration the drug. The lowest readings were usually found ithin five minutes of injection and thereafter the blood-essure returned slowly to base-line values. Oscillo-etric readings generally decreased slightly in amplitude. here was no clear correlation between blood-pressure ad skin-temperature changes. In 1 patient receiving 1·5 mg. per kg. the blood-pressure fell from 115/70 mm. Hg to 80/40 and the patient felt dizzy; this was the only instance of unpleasant subjective effects. Because of this incident, doses above 1·5 mg. per kg. were not used.

Of the 4 patients given the drug more than once, 3 responded to a dose of 1·25 mg. per kg. which several days previously, under apparently similar conditions, had been without effect.

Apart from transient increases at the time of injection no changes in pulse-rate were observed. Obvious sweating did not occur and in only a few cases was there slight flushing. The size of the pupils was unchanged and accommodation was never paralysed. No postural hypotension was found at the end of the experiments.

SUMMARY

One of a new series of ganglion-blocking diammonium compounds has been tested in normal volunteers. A safe dose has been determined, but this dose is not constantly effective even in the same person.

We are grateful to Mr. W. Arthur Mackey for his encouragement and interest in this investigation; to Dr. James Bell for his advice; and to Dr. Gerard Lorriman and Ciba Laboratories for supplies of the drug.

A. G. BAIKIE
M.B. Glasg.
Late House-surgeon

J. R. SMITH
M.B. Glasg.
Surgical Registrar

Surgical Unit,
Southern General Hospital,
Glasgow

Reviews of Books

ntoward Reactions of Cortisone and A.C.T.H.

VINCENT J. DERBES, M.D., F.A.C.P., associate professor of medicine, and THOMAS E. WEISS, M.D., instructor in medicine, Tulane University of Louisiana. Oxford: Blackwell Scientific Publications. 1952. Pp. 51. 8*s*. 6*d*.

THIS is an admirable little book, short, to the point, p to date, and containing plenty of references should the eader desire to pursue any topic further. Those who use ortisone and A.C.T.H., and have not had time to keep up ith the tide of published work on the unwanted effects f these powerful hormones, must certainly buy and read his book. Hæmorrhage from the gastro-intestinal tract the only serious omission from the listed reactions. ost-cortisone suicide, though rare, should also have been ncluded. Apart from these and the curious use of of" in the title, there is nothing to criticise.

a spondylarthrite ankylosante

J. FORESTIER, F. JACQUELINE, and J. ROTES-QUEROL. Paris: Masson. 1951. Pp. 330. Fr. 2650.

THIS book presents a complete clinical picture of nkylosing spondylitis, with all available X-ray informa-ion, as well as an interesting account of the histological indings with studies of dried bones. It ends with a hapter on treatment. A short chapter on clinical xamination, although it contains nothing fresh, deserves raise for its simplicity. Most of the work consists of a etailed study of the symptoms attributable to different arts of the spine and to peripheral joints, with some irst-class X-ray photographs, one depicting a sacro-iliac oint outlined with tin. The authors have collected 400 ases, and have followed up 40 of them for more than wenty years. A quarter of these were seriously crippled; o the opinion is expressed that treatment may not only elieve the symptoms but improve the prognosis. The linical section is based on the study of 200 cases. An nteresting chapter is devoted to a senile form of "anky-osing hyperostosis." Like much of the book, it is care-ully set out but not really relevant: new ideas on etiology are not forthcoming, and indeed could hardly be expected. A useful table shows the difference between the sacro-iliac joint in tuberculosis and ankylosing spondylitis. Corticotropin and cortisone are abruptly dismissed in three pages, which detracts from the value of the book. It would gain elsewhere by being drastically shortened; but it is a good piece of work, and welcome.

Management of Bronchial Asthma

HERBERT G. J. HERXHEIMER, M.D. Frankfurt, L.R.C.P.E., research assistant, University College Hospital Medical School, London; formerly professor of medicine at the University of Berlin. London: Butterworth. 1952. Pp. 107. 22*s*. 6*d*.

As he explains in the preface, the author has two reasons for writing this book; the first is his increasing interest in asthma, and the second his wish to guide the medical practitioner through the forest of therapeutic procedures to those he himself has found valuable.

Some will quibble at his definition of bronchial asthma as "a transient and usually repeated attack of breathlessness caused by bronchial obstruction." Endobronchial tuberculosis or bronchial carcinoma may at some stage produce these symptoms, but they bear no relation to the clinician's concept of asthma, in which, basically, it is the variation in the calibre of the terminal bronchioles, on inspiration and expiration, which by check-valve action traps the air in the alveoli. Dr. Herxheimer says he knows of no case of clinically proved emphysema in which asthma is not present, and again many would not agree with him in this.

His classification of the ætiology and of the clinical types of asthma is somewhat vague and gives little importance to respiratory infection as a cause. He suggests that in asthma brought on by excitement, overbreathing with loss of carbon dioxide is an important factor.

He draws attention to the suggestibility of asthmatics, and the temporary improvement obtained by a new treatment or a new doctor; but he is pessimistic about "cure" for most cases, believing that palliation of symptoms is all that can reasonably be expected. He uses spirographic records in the investigation and assessment of treatment and many of these interesting tracings are illustrated in the book.

Little practical advice is given on the avoidance of environmental allergens, and he is not enthusiastic about hyposensitisation by injection. He uses inhalation of the allergen as aerosols for this purpose, but admits that this is time-consuming and only practical for an expert.

Much of the book deals with the treatment of asthma by means of drugs; Dr. Herxheimer favours isopropyl noradrenaline, as an aerosol in 1% solution rather than by mouth, and finds that the anti-histamines have real value, though the particular drug and dose varies with individual cases. Promethazine ('Phenergan') 50-150 mg. taken about 1½ hours before bedtime may prevent the usual nocturnal wheezing, and the fatiguing effect may be negligible. After reviewing recent papers, he concludes that A.C.T.H. and cortisone do not cure asthma but may be very valuable in acute attacks of status asthmaticus, although the mode of action is unknown. Treatment of bronchial infections by antibiotics is scarcely mentioned.

He recommends expiratory breathing exercises for chronic or persistent asthma, but not for occasional attacks; for he believes that the breathing apparatus is in fact trained by these periodic attacks. This belief is not shared by all: the asthmatic paroxysm causes over-inflation of the lungs, whereas the object of breathing exercises is to train the patient to deflate the chest.

Readers would have welcomed some facts on the long-term results of treatment of asthma from Dr. Herxheimer's great clinical experience. As it stands, the book chiefly offers guidance on the palliative treatment of asthmatics.

The Normal Cerebral Angiogram

ARTHUR ECKER, M.D., PH.D., surgical neurologist, Syracuse, New York. Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 190. 47*s*.

Dr. Ecker tells us nothing about the source of his material, except that he describes himself as a surgical neurologist of Syracuse, New York. To judge by this comprehensive book he must have considerable experience in cerebral angiography. His technique may not commend itself fully to all workers in European countries, but it is practical and adequate. If compression of contralateral vessels were not so much stressed, and the technique allowed of anteroposterior and lateral projections without movement of the patient's head, there would be little to criticise. Difficulties and possible complications of the procedure are very clearly set out. The normal anatomy of the cerebral vessels and its variations are admirably described and illustrated by excellent X-ray reproductions and diagrams. The book may be read with profit both by the specialist worker and by those whose contact with the subject is only occasional. It is something of a challenge to the neurological radiologist to consolidate his position by enlarging his experience, in collaboration with his neurological and neurosurgical colleagues.

Biological Effects of the External Beta Radiation

Editor: RAYMOND E. ZIRKLE, professor of radiobiology, Institute of Radiobiology and Biophysics, University of Chicago; consultant, division of biological and medical research, Argonne National Laboratory. London: McGraw Hill. 1952. Pp. 242. 28*s*.

SOME of these papers on radiobiological work done in the United States during the late war have already been published. The aim, the preface states, has been to publish the information in book form as quickly as possible; and the editing has certainly not been very severe. Specialists in the subject, however, will find much of interest, particularly on the general biological effects of ionising radiations.

One of the main problems in radiobiology is the reason for the death of animals after over-exposure to penetrating radiation. A number of factors undoubtedly play a part—for instance, toxic products from damaged tissues, blood changes, hæmorrhage, and infection. The experiments reported here yield the surprising result that the mean lethal dose of superficial beta radiation for a number of species corresponds approximately to the same amount of radiation energy absorbed per unit volume of animal. This would indicate a much simpler lethal mechanism than is the case with penetrating radiation: it argues in favour of the production of a toxin and similar response of different species to equivalent concentrations of such a substance, though this hypothesis gains no support from certain other studies.

The sequelæ of beta irradiation are similar in many ways to those of thermal burns, though the period for the development of symptoms is longer. Loss of plasma is reported, but there is no corresponding increase in the value of the hæmatocrit. Presumably with beta irradiation the changes take place slowly enough for the compensating mechanisms to keep step with the injury. The recovery-rate following beta irradiation was found to be more rapid than that following the acute lethal effects of penetrating radiation, but slower than that which has been observed with X rays when erythema of the skin has been the criterion.

Experiments carried out on a combination of superficial and penetrating radiation indicate that, so far as acute lethal effects are concerned, the two types of radiation are not fully additive, though this may be because the beta and gamma irradiations were not given simultaneously or with the same duration of exposure. Work on tumour induction suggests that in rats and mice a relatively heavy dosage of beta radiation is followed by an increase in the rate of appearance of both superficial and subcutaneous tumours. In rats the increase was much greater than in mice, indicating a species effect. No tumours were observed over the time of experiment in the guineapigs or rabbits treated. A carcinogenic effect was also found in rats and mice when the radiation was given in daily doses. The results differed from those when single doses of beta radiation were given in that only subcutaneous tumours were observed. There is at the moment no explanation for this difference.

The book is lithoprinted with clear tables and figures, and illustrated with photographs, technically good, of animals mostly in extremis. It is to be hoped that, in future experiments of this nature, animals will not be allowed to reach such an appalling state. All observations of any scientific value would have been made long before some of the animals had reached the condition shown.

Applied Anatomy for Nurses

E. J. BOCOCK, S.R.N., S.C.M., D.N.; R. WHEELER HAINES, M.B., D.SC., F.L.S. Edinburgh: E. & S. Livingstone. 1951. Pp. 320. 15*s*.

THESE authors have given serious thought to the problem of how much anatomy should be imparted to nurses in training. The fifteen chapters describe the structure of the body, presenting those facts which will be useful to the nurse in her work, and not burdening her with details only necessary for a surgeon or diagnostician. The information is entertainingly given, and the influence of structure upon function, and the bearing of both on symptoms, are kept constantly in mind. The book should make absorbing reading for the keen student nurse. The illustrations are clear, informative, and well labelled, and much of the success of the book depends on them. In the next edition the artist's name should appear on the title page.

Doctor Viper: *The Querulous Life of Philip Thicknesse* (London: Cassell. 1952. Pp. 332. 21*s*.).—This book, though interesting and amusing, never quite catches the spirit of Dr. Philip Gosse's introduction. One day chance caused Dr. Gosse to look up in the *Dictionary of National Biography* the account of the life of that gentle, lovable poet and physician, the inventor of the famous biscuit, Dr. William Oliver of Bath. He found that once and only once did he have a quarrel, and that with a man called Philip Thicknesse. Dr. Gosse followed up the clue and in Thicknesse has resurrected an 18th-century much-married man of character, an eccentric with a gift for quarreling and for making offensive personal remarks in an age when full-blooded public slander was something of an art. A champion of the underdog, he can claim fame because he discovered and encouraged the genius of Thomas Gainsborough. He was a soldier, a gossip, a traveller, and a writer who met and quarrelled with persons of all classes, including John Wesley and an Archbishop of Canterbury. He wrote down and published his squabbles without the slightest regard to the law of libel, and they make spicy reading. Here is a sample: "I will not call this doctor a beast, a reptile, an assassin and a murder-monger, but the reader will, I am sure, excuse me in saying he is a base libeller, a liar, and a wicked defamer and has no pretentions to be considered a gentleman." Small wonder was it that Thicknesse was nicknamed "Dr. Viper." The book is written with all Dr. Gosse's charm and it does not seem to be his fault that his eccentric doesn't quite come to life. Probably it is Dr. Viper persisting in being awkward.

THE LANCET

LONDON: SATURDAY, JUNE 7, 1952

Sequel to the Award

ALL general practitioners in the National Health ervice should have received this week a report on he Danckwerts adjudication, and the recommendations of the Working Party on the future distribution f the practitioners' central pool of remuneration. his document (whose terms are set out on p. 1155) as been circulated by the General Medical Services ommittee for local discussion before a Special onference of Local Medical Committees on June 26. his conference will be asked to endorse the recommendations of the Working Party, and to request hat steps be taken to implement the Danckwerts ward.

The award by Mr. Justice DANCKWERTS makes it lear that he was satisfied that the general practitioners had been substantially underpaid ever since he health service began. It appears, from the alculations set out in the G.M.S.C.'s document, hat the extent of this underpayment has increased ear by year. Three main factors have contributed o this. The first was that the amount of money in the entral pool remained substantially the same despite considerable increase in the number of general ractitioners in the service. The second was that he central pool, which provides gross remuneration, emained the same despite steadily rising practice xpenses. Both these factors have been recognised by the Adjudicator. He has recommended, and the Government have accepted, that in future any variation in the number of doctors and in the size of practice expenses shall be taken into consideration n determining the money required year by year in he central pool. A third factor had to be considered by, the Adjudicator—namely, betterment. The basis of the practitioners' claim was the Spens report; and this report expressed the practitioners' range of remuneration in terms of 1939 money values. The Adjudicator, in determining the proper sum for the financial year 1950–51, applied a betterment figure of 100%; and he indicated that in his view the corresponding figure for 1948–49 was 85%. The G.M.S.C. had hoped that, these two figures having been accepted, it would have been possible to negotiate some intermediate figure for 1949–50, and to reflect any further variation in money values when determining the size of the central pool for years subsequent to 1950–51. Here, however, the Government have not been able to agree. They could not "insulate" in this way one particular section of the community from all future fluctuations in the cost of living. They have therefore decided that "in pursuance of the Danckwerts award the central pool should be calculated on a betterment factor of 85% for 1948–49 and 1949-50 and of 100% for 1950–51 and subsequent years."

The Working Party was asked to suggest a new way of distributing the central pool that would do four things—discourage unduly large lists, improve relatively "the position of practitioners least favourably placed under the present plan of distribution," facilitate the entry of new doctors into practice, and stimulate group practice. With the additional demands brought by the new service, the efficient handling of a practice of 4000 patients has thrown a heavy burden on single-handed practitioners. Until now however, the achievement of an income in any way approaching the top of the range recommended in the Spens report was impossible with a list far short of 4000. Had the Adjudicator's award been less favourable, the Working Party might have had to recommend no alteration in the permitted numbers, but might instead (to satisfy their terms of reference) have had to suggest a substantial taper in the capitation fee for the last 1000 or so patients on the permitted list, so as to make the acceptance of this group relatively much less profitable. As, in the event, the award was large enough to allow of an appreciable reduction in numbers without bringing about a serious fall in the incomes of practitioners with large lists, the Working Party preferred to recommend an outright reduction in the permitted number, bringing the maximum list of a single-handed practitioner from 4000 to 3500, and that of a doctor with an assistant from 6400 to 5500. This will necessitate reduction of some of the larger practices or the employment in them of extra partners or assistants. This, in itself, will create openings for many new entrants. Some, with the help of the new initial practice allowance, will set up independently in practice in under-doctored areas. More will probably be taken into partnership by established practitioners. The Working Party has suggested that an appreciably loaded capitation fee shall be paid for patients in the range 501–1500. In a partnership extra loaded capitations can accrue to each partner, but no such load is to be applied in respect of patients cared for by an assistant. The result of this provision would be that a doctor with a practice of 3000 patients or more would increase the practice income by £500 per annum by taking a partner. This proposal should supply both the means and the inducement for offering a partnership to an assistant, neither of which are afforded by the present scheme of distribution.

The Conference of Local Medical Committees had previously suggested that there should be loading of the first 1000 capitation fees. Objection was made to this suggestion on the ground that an appreciable amount of the money available for loading would be paid to doctors with lists below 500, many of whom were not seeking to take their full share of the work of general practice in their area. Some, perhaps had restricted lists, or were concerned solely with the medical care of hospital staffs, while others were giving occasional help in their husbands' practices. Those with lists below 500 will, of course, include many who are genuinely seeking to make their way in general practice; but they should be helped either by the initial practice allowance or by the load accruing to the practice if they are being made partners. In addition there will be some doctors (often elderly) with small lists, who, because of their age or the nature of the area in which they work, cannot expect to see their practices grow appreciably.

At present they commonly receive a fixed annual payment, and the withdrawal of this might mean considerable hardship. At the suggested level of loading they will need to have a list of at least 800 in order to be no worse off than before the award. Therefore the Working Party, which was asked "to bring about a relative improvement in the position of those least favourably placed," has assigned £50,000 per annum as a subsidy for them. Experience will show whether this is enough.

These new financial arrangements are likely to promote the development of partnerships and group practices; but the Working Party has also agreed to set aside a yearly sum of £100,000 to be used, if need arises (in ways still undefined), to stimulate group practice. Thus it seems that in a commendably short time the Working Party has produced a scheme that goes far to satisfy its terms of reference. It should be noted, however, that the scheme tends to level both the work and the rewards of general practice. We welcome the reduction in the maximum size of lists, and indeed wish that it had been possible to carry this further. On the other hand, both this reduction and the method of distribution will make it easier for a greater number of doctors to approach the top of the improved remuneration scale. This underlines once again the need to evolve some method of rewarding special merit—a problem that seems to have been considered, but which has not been solved, by the Working Party. General practice, no less than the specialties, needs a leavening of exceptionally able men and women; and exceptional ability often needs to be attracted by the prospect of exceptional reward. In this light the formation of a College or Faculty of General Practice should not be long delayed.

New Light on Histoplasmosis

THE history of histoplasmosis may be divided into two periods. The first began in 1906 when DARLING,[1] working in Panama, described three cases and the causative organism, which he thought to be a protozoon and named *Histoplasma capsulatum.* The second period begins in 1941, when ZARAFONETIS and LINDBERG [2] and VAN PERNIS et al.[3] described a specific cutaneous test. In the first period the disease was regarded as extremely rare and invariably fatal. Nevertheless, in this period much knowledge was accumulated.[4–6] The causative organism was recognised as a yeast-like fungus by DA ROCHA-LIMA [7] and grown on various media from blood and from the spleen by DE MONBREUN [8] and HANSMANN and SCHENKEN.[9]

In tissues the organism takes the form of round or oval yeast-like bodies, which stain well with most nuclear stains and are weakly gram-positive and slightly acid-fast. At room-temperature it grows on various media in mycelial form, but at 37°C it grows in the yeast-like form on media rich in protein. CONANT [10] an NEGRONI [11] have successfully converted the myceli into the yeast-like form. The common symptoms o the disease are: irregular fever, ulcerative lesion of the skin and/or mucous membranes of mouth an pharynx, and local or general lymphadenopathy Usually the spleen and the liver are enlarged. Pulmonary symptoms and signs are common, consistin in cough, râles, sounds of pleural friction, and miliar opacities on radiographic examination. Anorexi is usual; diarrhœa and vomiting are fairly common and occasionally there is hæmorrhage from the gastrointestinal tract. The necropsy findings greatl resemble those in tuberculosis. The tissues reac to infection with *H. capsulatum* by formation o granulomatous lesions with epithelioid cells, gian cells of the Langhans type, and commonly caseou necrosis. Occasionally small granulomata consis of fibroblasts, lymphocytes, and plasma cells wit a few large mononuclear cells, or the lesion may b a minute area of necrosis surrounded by mononuclear cells. All organs may be involved, bu lymph-nodes, spleen, suprarenal glands, and lung are particularly affected. Ulcers in the gastrointestinal and upper respiratory tracts are commonl found. *H. capsulatum* is usually easily demonstrate in tissue sections. So far only about 200 cases o death from histoplasmosis have been described but in 6 there was histological evidence of Hodgkin' disease.[12] In 2 further cases leukæmia was found and in another 2 the histological diagnosis wa "*malignant reticulosis.*" *At present it is uncertai* whether the tissue reaction to histoplasma ma initiate malignant lymphogranulomatosis, or whethe patients with Hodgkin's disease have an increase *susceptibility to histoplasma infection.*[13]

The intradermal histoplasmin test opened a new line of research which resulted in the discovery of many mild and latent cases of histoplasmosis. Previously investigators in certain areas of the U.S.A. had made the puzzling observation that a high proportion of people with pulmonary calcification did not react to tuberculin. This was thought to be due to disappearance of tuberculin sensitiveness after healing of a tuberculous process. Such an explanation was, however, unsatisfactory because positive anergy in people with healed tuberculous lesions can be easily converted to allergy by tuberculin inoculation, in contrast to the negative anergy of generalised miliary tuberculosis, measles, and cachexia. Furthermore, this explanation did not account for the distinct geographical variations in the proportion of tuberculin-negative people with calcified foci in the lungs. The real explanation was found when all these tuberculin-negative people proved histoplasmin-positive. The histoplasmin test is highly specific. It gives weak cross-reactions with some other fungal antigens, but cross-reactions with tuberculin are extremely rare. The histoplasmin test provided the means for a thorough study of the geographical distribution of histoplasma infection. This has been carried out mainly under the auspices of the Tuberculosis Division of the

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1. Darling, S. T. *J. Amer. med. Ass.* 1906, **46**, 1283.
2. Zarafonetis, C. J. D., Lindberg, R. D. *Univ. Hosp. Bull., Ann Arbor*, 1941, **7**, 47.
3. van Pernis, P. A., Benson, M. E., Holinger, P. H. *J. Amer. med. Ass.* 1941, **117**, 436.
4. Parsons, R. J., Zarafonetis, C. J. D. *Arch. intern. Med.* 1945, **75**, 1.
5. Miller, H. E., Keddie, F. M., Johnstone, H. G., Bostick, W. L. *Arch. Derm. Syph.* 1947, **56**, 715.
6. Cawley, E. P., Curtis, A. C. *J. invest. Derm.* 1948, **11**, 443.
7. da Rocha-Lima, H. *Zbl. Bakt.* 1913, **67**, 233.
8. de Monbreun, W. A. *Amer. J. trop. Med.* 1934, **14**, 93.
9. Hansmann, G. H., Schenken, J. R. *Amer. J. Path.* 1934, **10**, 731.
10. Conant, N. F. *J. Bact.* 1941, **41**, 536.
11. Negroni, P. *Rev. Inst. bact., B. Aires*, 1940, **9**, 239.
12. Murray, J. P., Brandt, F. A. *Amer. J. Path.* 1951, **27**, 783.
13. Rodger, R. C., Terry, L. L., Binford, C. H. *Amer. J. clin. Path.* 1951, **21**, 153.

S. Public Health Service, and the W.H.O. Tuber- losis Research Office. The results are summarised nd discussed in an important paper by MOCHI and DWARDS.[14] Although information was lacking from any parts of the world, it was possible to draw a ap of the world distribution of histoplasmosis nd/or histoplasmin sensitivity. This shows the rgest area of histoplasmin sensitivity in the east- entral part of the U.S.A., centred on the lowlands t the junction of the Mississippi, Missouri, and hio rivers, with further areas in southern Mexico, entral America, and certain parts of South America. n isolated area of low sensitivity was found in outh Africa, but hardly any histoplasmin sensitivity n Europe with the possible exception of Italy. In reat Britain histoplasmin sensitivity has been tudied in students, men in the Royal Air Force, nd children in Wales and London.[15 16] None of hose tested reacted to intracutaneous injection of istoplasmin. The only reported case of histo- lasmosis in England was in a soldier who had been tationed in India and in the Sudan.[17] MOCHI and EDWARDS conclude that the geographical distribution f histoplasmosis and histoplasmin sensitivity suggests n association of the fungus with large rivers running hrough relatively low country. With increasing distance from the river and concomitant increase in altitude the frequency of histoplasmin reactors tends to fall. Man-to-man infection has never been demonstrated, and although histoplasmosis occurs in various domestic and wild animals transmission from animal to man has never been verified. It has been suggested that *H. capsulatum* is disseminated by flood-water carrying a soil-fungus mixture which later becomes airborne; recently EMMONS[18] has isolated the fungus from soil.

Histoplasmosis is an exquisitely endemic disease. Clinicians in histoplasma-free countries should, however, bear in mind that infection may be acquired by handling imported goods contaminated with dust containing the fungus. Infection with *Coccidioides immitis* has been transmitted in this way.[19]

Our Crime-sheet

THE theory that men are naturally moral, and that given reasonably just and secure conditions of life they will behave well, is not at the moment very easy to support. Sir SYDNEY SMITH, professor of forensic medicine in the University of Edinburgh, enumerated recently[20] the reasons why—if conditions of life are the decisive factor—we should now have a dwindling crime-sheet in this country. In the last fifty years we have seen, in medicine, a fall in the death-rate, a rise in the expectation of life, and a much-reduced infant mortality. We have gained control over many diseases and learned much about nutrition. Among social changes we have ensured higher wages, more food, less unemployment, better working conditions and—by and large—better standards of housing; we have put primary, secondary, and even university education within reach of all able minds; we have offered more opportunities for young people to take part in sports and pastimes; the cinema and radio have opened new doors to learning and enjoyment; the treatment of offenders has become progressively more enlightened, and, with the young especially, the emphasis is now on reform rather than retribution. Yet the number of serious crimes—not such trivial things as traffic offences, but violent crimes such as assaults and murders, dishonest crimes such as housebreaking, robbery, and theft, and sexual crimes such as rape and assault on females—has risen alarmingly. In England and Wales indictable offences known to the police have gone up from something under 100,000 a year in 1900, to 500,000 now. Sir SYDNEY did not mention the considerable rise in population over that time—from some 32,500,000 in 1901 to over 43,700,000 in 1951; but even if this is taken into account the serious-crime rate has risen from 3 per 1000 population in 1900 to 11 per 1000 today. He pointed out that there was only a slight rise during the first quarter of the century—hardly more than proportional to the increase of population. The first disproportionate rise—not at first very large—was between 1925 and 1929; and for the past twenty years the rises have been continuous. He is struck, too, by the enormous increase in cases of wounding and assault. In the first fourteen years of the century the annual average remained between 1300 and 1500. During the 1914–18 war it fell to half that figure, and it only reached its pre-war average in 1930. Since then it has risen rapidly until, in 1950, it reached 5650, five times the incidence before 1930. Crime has increased among both males and females—though, as always, the great majority of those found guilty in the courts are males. Drunkenness, on the other hand, has declined remarkably in the past fifty years; so drink cannot be blamed for the rise.

The peak ages for crime, as we know by this time, are in youth rather than in middle or old age; but the age-distribution is particularly depressing at present. In 1950, of 73,000 convicted of larceny 46% were under 21, and nearly half of these were under 14. Of 20,000 convicted of breaking and entering, a third were under 14; and even with sexual offences, a fifth of those convicted were under 17. Out of every 100 boys in the country aged 14, 2 were convicted of serious crime in 1950. This high rate of crime among juveniles is a comparatively new thing. Up to about 1930 there was little difference in the crime-rate in those under 16 and those over 16. After that date the rate in the under-16 group rose steeply, while the rate in the over-16 group remained much the same. Sir SYDNEY takes this to mean that the problem of juvenile delinquency first began to assume serious proportions in 1928–30, and that it preceded the increase in the incidence of crime in general. About 80% of juveniles convicted of an indictable offence for the first time do not come into court again, and we may suppose that with them our reformative efforts are successful. Many of the remaining 20% are sent to borstals or reformative prisons, and some are in fact reformed; nevertheless, more than half the boys sent to borstals are reconvicted within a few years.

Summing up the position, Sir SYDNEY said that juvenile crime does not seem to have been favourably affected by our attempts at reform and rehabilitation.

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[14] Mochi, A., Edwards, P. Q. *Bull. World Hlth Org.* 1952, 5, 259.
[15] McCracken, B. H. *Thorax*, 1948, 3, 45.
[16] See leading articles, *Lancet*, 1949, i, 67, 228. McCracken, B. H. *Ibid*, p. 284. Evans, P. *Ibid*, p. 270.
[17] Derry, D. C. L., Card, W. I., [illegible]n, I., Duncan, J. T. *Ibid*, 1942, i, 224.
[18] Emmons, C. W. *Publ. Hlth* [illegible] 1949, 64, 892.
[19] Skinner, J. [illegible] 743, 482.
[20] In [illegible] Dundee,

but on the contrary has increased considerably; and this suggests that antisocial behaviour-patterns may have become fixed long before the children get into the hands of the police. Delinquency is the result of a whole group of factors, some personal to the child, some to the parents, and some to the surroundings in which the child lives. Because the major rise in crime began at the time of the severe general depression in 1930, we have been apt to think of economic hardship as a cause; but, as he remarked, the progressive fall in unemployment since the late '30s has not been associated with a fall in crime: on the contrary. Overcrowding is also blamed, but it is doubtful whether this is any worse today than it was in the early years of the century. He attaches little importance to the cinema, or the instability of adolescence, as causes of crime: neither can explain the sudden rise from 1930 onwards. We must look deeper.

There is nothing, he says, to suggest that a child is born either a saint or a sinner; but he *is* born aggressive and acquisitive, and is thus potentially criminal. Growing up in a normal family, he learns to curb the antisocial parts of his nature; conscience slowly develops and reinforces the desire to conform to the moral and social pattern around him. This conditioning in the home is largely undertaken by the mother; and bad family training may mean poor standards and a weak, elastic conscience. "Criminals are therefore to a great extent developed in the nursery." Of course bad home training may be counteracted at some stage by good teachers or good companions; but it may equally be reinforced by bad ones. For most juvenile delinquents the early training given has been deficient; and it is often so, he feels confident, because the children are growing up in homes where the parents have no particular belief or code of morals: man has lost his faith not only in his religion but in his parents, his teachers, and his leaders; and science, he thinks, can give nothing in exchange. "The spiritual chaos in which we live and our failure to build into society any unified meaning of life is to my mind a most serious factor in the upbringing of youth, and I see no way in which we can combat it." We are getting the results of two wars. The 1914–18 war disrupted family life, sent the fathers to the front and the mothers into factories, and imbued everybody with a strange excited belief that none of the ordinary things mattered. Ten to fifteen years later, we harvested this sowing: the children born in the war and in the restless '20s showed their lack of sound home training in the greater delinquency-rate of the '30s. Now, as parents themselves, they have suffered the impact of a second war; and we may expect among their children, Sir SYDNEY believes, a further increase of delinquency in the next few years. His anxiety will be shared by many who wish to think well of humanity but are disconcerted to find that principles unbacked by religious belief are unexpectedly difficult to hand on to the young: they may keep much of their force in the first generation but are apt to become progressively attenuated in the second and third. Some such debasement of th
moral currency seems to be going on toda
parts of the world. Moreover wo
tingly done some harm, he th

schools, free meals, and youth clubs. These th
good in themselves, tend to reduce the parents' s
of responsibility for their children's care and discip
The value of discipline, especially, is being too n
disregarded: "a child must learn, as must the a
that bad behaviour will result in some kind of disc
fort to himself." Sir SYDNEY might have pointed
moreover, that this kind of lesson, to be effective, n
be immediate and personal. The whole human rac
the moment, is suffering a good deal of discomfor
account of bad behaviour, but no groups within it
seriously examining their own conduct to see
much of the blame lies at their own door.

This masterly diagnosis of our state was
unfortunately, backed by a specific remedy, tho
he suggested some palliatives. Doctors, teach
nurses, and others should try to find the maladju
child at the earliest possible moment, and get
treated. Parents should feel responsible for trai
him (but who is to train the parents?). Researc
needed into the early manifestations of antiso
conduct in infancy and childhood. These are all g
ideas, certainly; but perhaps what the growing c
and his parents need is some vision of a world wor
of good citizenship, and some inner reason for striv
to build it.

Annotations

A.C.T.H. AND THE PIGMENT HORMONE

THE fascinating way in which certain amphibia, fis
and reptiles change colour to match their surroundi
has long been the subject of study. The chameleo
coat of many colours is, of course, the best-kno
example, but to a lesser extent frogs and toads posses
similar mechanism; in light, dry, and warm surroundi
they turn a pale green or tan colour, but in dark, mo
and cold surroundings they darken almost to blackn
This change is the work of the melanophore, a melan
bearing amœboid cell which, by extending or contract
black tendrils among the other cells of the animal's sk
alters the amount of reflected light and hence the appar
colour. Hogben[1] showed, for amphibia at least, th
these melanophores were under direct hormonal cont
that the hormone came from the pituitary gland, a
that it could be found in the pituitary glands of all ty
of vertebrates, most of which do not, of course, poss
specialised melanophores. Methods of chemically puri
ing this hormone and of determining its origin have sin
been studied.[2] [3] Most early workers used as their sour
an extract or a dried powder prepared from posteri
pituitary gland. Hogben and others found, howev
that although the posterior pituitary was apparent
the best source of the hormone, significant amounts cou
also be isolated from the anterior pituitary. Anatomic
and other considerations have led to the belief that t
pars intermedia of the hypophysis is in fact where mo
of the pigment hormone is produced[2]; hence th
hormone has been named "intermedin."

The function of intermedin in animals with no melan
phores was unexplained, but new work in Sweden an
Israel now gives very convincing evidence that inte
medin and A.C.T.H. are one and the same.[4] [5] These repor
confirm th rvation of Sprague et al.[6] that A.C.T.

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1. H entary Effector System. Edinburgh, 1924.
Quart. J. exp. Physiol. 194
014, 32, 121.
286.
ort, A
rry, L. L., Binford, C. H. b, C. J
21, 163.

is very powerful melanophore-dilating properties in ogs; this activity could not be dissociated from renocorticotropic-activity in the various preparations hich were tried, including Li's A.C.T.H. peptide. More- ver, in conditions where an increased amount of circu- ting A.C.T.H. would be expected, such as Addison's isease, and in conditions of stress—e.g., after an peration or a myocardial infarction—patients' serum owed an increased power to expand melanophores. vidence pointing in the same direction is given by older bservations that intermedin could cause hypertrophy f the adrenal cortex.[7 8]

A.C.T.H. is, of course, a hormone derived from the nterior pituitary gland: intermedin is said to come from he pars intermedia. This anomaly is unexplained if the rmones are in fact the same. Dr. F. G. Sulman, in letter published in this issue, describes a method for he assay of A.C.T.H. in blood, based on the assumption hat they are identical. His method involves the separa- ion of an A.C.T.H.-containing fraction of blood, and the ssay of its melanophore-expanding activity, in light- dapted frogs. Should further work prove that this test oes in fact measure A.C.T.H., its value will be great; for nlike other methods it seems not only reliable but imple and cheap. In another paper Sulman[5] calculated hat as little as 0·001 µg. of A.C.T.H. will cause darkening f the skin in light-adapted frogs. Moreover, the response an be assessed by measuring microscopically the xpansion of individual melanophores in the web of the rog's foot. When the effect has worn off the frog can be used again; hypophysectomy of the animals (a procedure which is not well tolerated, except by xenopus toads) does not seem essential, but can be done to prevent interference by endogenous hormones. Such a method of assay, applicable as it is to small amounts of serum, will have obvious uses in studying, more quantitatively than has hitherto been possible, the part played by the human pituitary in many situations—e.g., the response of the body to trauma or disease, and the mechanism of salicylate therapy in rheumatic fever.

Sulman has also indicated another aspect of the A.C.T.H.-intermedin picture—namely, that A.C.T.H. may cause skin pigmentation in man. We must distinguish here between the darkening of frogs, which is the result of the expansion of individual melanin-bearing cells, and the darkening of man, which is presumably caused by an increase either in the amount of melanin in the specialised cells that make it, or in the number of the cells themselves. Whatever the mechanism, it has been repeatedly noticed that patients receiving A.C.T.H. for more than a few weeks become pigmented, whilst patients on cortisone do not. In addition a pigmented or swarthy skin is a feature of certain conditions where increased adrenocorticotropic activity of the blood is known or suspected—i.e., Addison's disease, pituitary basophilism, and pregnancy. Thus pigmentation of the skin in Addison's disease becomes analogous to myxœdema of the connective tissue in primary hypothyroidism[9]—a direct effect of an excess of a pituitary hormone deprived of its target organ.

CAMPAIGNS AGAINST YAWS

THE first International Symposium on Yaws Control was held in March at Bangkok, under the auspices of the World Health Organisation. The meetings took place in the Grand Palace; and there was later a field trip, excellently organised by the Thai government, in the region of Ubol in north-east Thailand, where the campaign of mass treatment with penicillin was inspected. The conference was attended by delegates of twenty-three nations; those from the United Kingdom included Dr. C. J. Hackett and Dr. R. R. Willcox.

W.H.O. has helped to organise a number of imaginative projects against the treponemal diseases, including those against yaws in Haiti, Thailand, and Indonesia; against endemic syphilis in the Balkans; and against bejel in Iraq. By the end of last year no less than four million people had been examined and over one million treated with penicillin in these large operations. The conference drew on the experiences of workers engaged in these projects, and it concentrated particularly on trying to define the unknowns in the disease. Although direct contact is the most usual mode of infection, the rôle, if any, of insect vectors must still be elucidated, as must the viability of the spirochæte in moist soil.

Treatment in the early stages is simple. A single injection of 1·2 mega-units of a repository penicillin will give reasonable hopes of cure and render the patient non-infectious. Possibly an even smaller dose may suffice, but so far the information does not justify its general use. Other antibiotics, such as aureomycin, terramycin, and chloramphenicol, are effective. The main difficulty, however, is not in treating the established case but in securing the cases to treat. Yaws is usually found at the end of the lines of effective communication in underdeveloped areas lacking permanent medical resources. In such circumstances mass methods of treatment are best; but experience is already showing that a single mass treatment is insufficient, since some cases are inevitably missed at the first visit, and infectious latent cases, those in the incubation period, and their contacts—as well as the relatively few treatment failures—will cause a recrudescence of the disease in the community. The minimum number of return visits, and the intervals between them, has yet to be determined. It is becoming increasingly apparent that contacts must be examined and treated. Some think of contacts as simply familial residents of the hut; but yaws is a disease of children, and children play with other children. Realistically, the term "contacts" implies the total child populace of the village, and probably the adult populace as well, and it may be necessary to treat all.

Many hope that these imaginative campaigns of yaws control presage the medical, social, and economic improvement of the undeveloped areas. Such a phase of consolidation depends ultimately on the effort of local health administrations.

FATTY LIVER IN INFANCY

A FURTHER contribution to the understanding of the nutritional origin of fatty and fibrotic changes in the liver has come appropriately from West Africa, where the name kwashiorkor originated. Silvera and Jelliffe[1] have been making liver biopsies in unselected small infants. Using a Silverman needle they chose the anterior subcostal approach whenever the liver was palpable, and if the liver edge could not be felt the puncture was made through the eighth right intercostal space in the mid-axillary line. In some cases examined post mortem liver "biopsy" was performed immediately after death because of difficulties in securing permission for necropsy.

The series consists of 13 infants under one year of age and 15 older children between one and eleven years of age. The main interest of the report lies in the younger group, for alterations in the liver amounting in some instances to "extreme generalized fatty change" were present in some of the specimens examined even in the first weeks of life. All the children in the series were from poor families. They were all breast-fed for varying periods, and suckling continued, as is customary among the Yoruba people, up to the age of one or even three years. These infants are weaned on to food which is almost exclusively carbohydrate. The result, now well recognised, is that soon after weaning is begun,

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[7] Holmquist, A. G. *Klin. Wschr.* 1934, 13, 664.
[8] Jores, A., Beck, H. *Z. ges. exp. Med.* 1934, 94, 293.
[9] Watson, E. M., Pearce, R. H. *Amer. J. clin. Path.* 1949, 19, 442.

[1] Silvera, W. D., Jelliffe, D. B. *J. trop. Med. Hyg.* 1952, 55, 73.

evidence of "malignant malnutrition" begins to show itself in some of the children. Silvera and Jelliffe, however, report instances of liver changes similar to those associated with malignant malnutrition in infants still at the breast who seemed otherwise normal from the nutritional aspect. A baby of ten days with ophthalmia neonatorum, and another of twelve days with thrush, showed extreme fatty changes in the liver. It is tempting in such instances to postulate a deficiency in the antenatal supplies to the fœtus. Similar changes found in *infants later in the first* year raise a different, but related, question with regard to the quality of breast-milk. In dealing with breast-feeding among Europeans, it is usually asserted that, whereas quantity may vary, the quality remains essentially the same as regards the main constituents. This has been said to be true even in famine conditions. Silvera and Jelliffe point out, however, that when the diet of the nursing mother is grossly deficient in protein, and when the infant remains at the breast for several years, the composition of the milk may be deficient; and they suggest that research into this problem would be helpful.

Examination of the older children in the series showed liver changes of the type previously reported; and these changes were essentially the same as in some of the youngest infants. Several babies in the series died of gastro-enteritis, and it is an important negative observation that in such cases the liver was either found to be normal or showed much less change than in the other infants in the series.

Even though maternal malnutrition may be a factor in the production of liver changes in these babies, Silvera and Jelliffe urge that early weaning should not be lightly advised, because the alternative is a worse diet of carbohydrate.

FUNGUS INFECTIONS OF THE FEET

THE incidence of tinea pedis is much higher in the Services, in sporting fraternities, and among miners than in the general population. This is partly because of the communal use of bathrooms and the sharing of footwear, and partly because the wearing of impermeable or heavy footwear for "foot-slogging" or vigorous exercise or as protection against wet and injury causes retention of sweat and maceration of the skin.

The incidence of tinea pedis among the general population is unknown because the mildly afflicted do not ask for medical attention. In the Forces and among students, however, surveys of fungus infections can be made with some precision. In the U.S.A. between 37% and 89% have been reported as affected. In this country, Davies[1] has examined 1050 soldiers and found 645 (61%) with clinical fungus infection. Among new recruits 33% were affected, but in men with 6–18 months' service the proportion rose to 76%, while in those with 1½–6 years' service it was 75%. Davies's figures include cases where the infection was minimal or slight, consisting of scaling and cracking between one or two toes. These cases are questionable; but, subtracting them, there remains a clear incidence of 23% in all groups and 11% in recruits. Walker[2] found a lower incidence among 1010 recruits examined; questionable signs were present in 12% and definite signs in 3%.

Two facts are of great importance. Firstly, a carrier may have no clinical signs of infection[3]; Walker found 9 carriers, all of *Trichophyton interdigitale*, among 39 recruits from whom positive cultures were obtained. Secondly, the presence of sodden, peeling, fissured skin in the clefts between the fourth and fifth toes does not necessarily imply fungus infection. Simple intertrigo from retention of sweat and chafing, brought on by crowding of the toes as a result of shrunken, impermeable socks and heavy footwear, can give a similar appearance; and secondary infection with banal-skin organisms may then cause an intertriginous dermatitis.

The organism most often responsible for tinea pedis i *T. interdigitale*, and the next most common organisms ar *Epidermophyton floccosum* and *T. rubrum*. *T. rubrum* is notoriously resistant to all forms of treatment Originating in South-East Asia, it was brought into thi country by many who served during the late war in South-East Asia. In adults it causes chronic desquamating lesions and often affects the nails; and reinfection of the skin from the diseased nails is one reason for the persistence of this type of infection. Rarely the infecting organism is not a fungus but monilia. It is likely that monilia can establish itself only when the balance of the skin bacterial flora has been disturbed in some way —for example, by excessive humidity or alkalinity, or from the use of certain antibiotics, or with diabetes mellitus.

Davies compared the therapeutic efficacy of Whitfield's ointment, Castellani's paint, 1% dithranol ointment, and brilliant-green. He found dithranol the most effective remedy, but at the same time the most likely to cause severe reactions. Castellani's paint was almost as effective, with occasional recurrences and milder reactions. Whitfield's ointment and brilliant-green were both relatively ineffective, and their use was often followed by relapses. The newer fungicides have not fulfilled early hopes. The use of phenyl mercuric nitrate for instance, is liable to lead to sensitisation; while zinc undecylenate is relatively ineffective. The best results follow application of Castellani's paint at night and a 3% salicylic acid powder in the morning, preceded if necessary by permanganate soaks and accompanied by the daily changing and sterilisation of socks. The treatment of boots and shoes with formalin is of doubtful value. The risk of recurrence is increased by hyperidrosis. The usual mode of transmission is uncertain; but Riddell[4] states that the majority of cases probably represent a recrudescence of infection following a period of local immunity, rather than a new infection by organisms living saprophytically on floors or baths. Our special need is for a fungicide effective against *T. rubrum*.

SERUM TESTS FOR SYPHILIS

THE diagnosis of early syphilis is usually clear-cut, taking into account the history, clinical signs, dark-ground examination for spirochætes in the lesions, and serum tests. Many of these patients seek treatment promptly; and the sera of two-fifths of them remain negative, while of those that become seropositive most return to negative fairly soon. With the residue, however —the Wassermann-fast reactors—the question whether treatment has been adequate has to be answered. In the last few years this question has been complicated by the employment of cardiolipin as the antigen in the Wassermann reaction; for this increases the sensitivity of the test so that in such cases the reaction remains positive longer.[5]

During the last decade a further problem has arisen, owing to the practice of subjecting relatively large sections of the population, such as blood-donors and pregnant women, to routine serum tests. *Inevitably* some of these people have a positive Wassermann reaction. Of 6809 antenatal patients tested in London during the years 1949–51 44 (0·64%) had positive serum tests.[6] Some of these "concealed Wassermann-positive reactors" have a history of treated syphilis; but in the absence of any clinical history or evidence of syphilis other than the positive blood test, diagnosis is difficult. Some

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1. Davies, A. J. *J. R. Army med. Cps*, 1952, 98, 99.
2. Walker, J. *Brit. J. Derm. Syph.* 1950, 62, 239.
3. Ajello, L., Keeney, E. L., Broyles, E. N. *Bull. Johns Hopk. Hosp.* 1945, 77, 440.
4. Riddell, R. W. *Brit. med. Bull.* 1951, 7, 197.
5. Price, I. N. O., Wilkinson, A. E. *Brit. J. vener. Dis.* 1952, 28, 16.
6. Price, I. N. O. Personal communication.

may have latent syphilis, while others may be non-syphilitic reactors (the so-called "biological false positive reactors"). Non-syphilitic positive reactors can be divided serologically into "acute" and "chronic." In the former group the positive reaction persists for three or four months, and in this country is associated often with infections of the upper respiratory tract, virus pneumonia, or pregnancy; while sometimes it is a sequel to vaccination for smallpox. Chronic non-syphilitic reactors may have a positive reaction for years, and differentiation from latent congenital syphilis or acquired syphilis is almost impossible if a serological response to antisyphilitic treatment is not evident.

With both these groups of patients the clinician has a dilemma in deciding whether treatment is needed. The history and physical examination have to be carefully reviewed. The technique of the serum tests should be above reproach, and parallel testing with the Venereal Diseases Reference Laboratory (Medical Research Council) should be considered. Even then, the diagnosis may remain in doubt. Now, however, there is one ray of hope—namely, Nelson's treponema immobilisation test.[7] Work in the U.S.A.[8] suggests that nearly 90% of non-syphilitic positive reactors can be identified with certainty by this specific test, which is being investigated in Britain, France, Denmark, and elsewhere.

RESIDUAL COMMON-DUCT STONES

MOST surgeons have had the mortifying experience of finding that a patient in whom they have removed the gall-bladder and drained the common bile-duct has developed a persistent biliary fistula or jaundice. The cause becomes only too obvious when the common duct is re-explored; one or more stones have been left behind at the operation. In this country the usual method of determining the presence of stones in the common bile-duct at the primary operation is palpation of the duct with a forefinger in the foramen of Winslow and a thumb over the free edge of the gastrohepatic omentum. This method has limited value, since the lower end of the common duct can be palpated only through the head of the pancreas, and it is at the lower end that stones are discovered at the second operation. As a rule, before finishing the operation by draining the duct, its patency is established by passing a bougie downwards through the ampulla into the duodenum; and it is generally held that if the bougie passes without difficulty, no stone has been left behind.

Mallet-Guy[9] believes that cholangiography on the operating-table, combined with manometry, may help to prevent this mishap. A cannula is passed into the common duct through the cystic duct, saline is injected, and tracings are taken of the pressure in the common duct as the saline runs in; then 10 ml. of iodised oil is injected through the same cannula and the biliary tree is radiographed. Mallet-Guy thinks that manometric pressure in the common duct of over 14 cm. of water indicates some biliary obstruction, while one of below 8 cm. of water indicates hypotonia of the sphincter of Oddi. He observes that in 100 patients with stones in the common duct who were operated on between November, 1948, and September, 1951, manometric and radiographic re-examinations after choledochotomy and removal of all accessible stones showed the biliary ducts hypertonic reactions of the sphincter of Oddi in 22, and absolutely free from stones in 54, residual stones in 12, obstruction from miscellaneous causes in 7. Mallet-Guy feels that the 12 stones would have been missed if this type of study had not been made.

The difficulty about accepting the value of manometry in this field is that we have no information about the normal pressure. The range which Mallet-Guy cites as normal applies to patients with biliary-tract disease in whom no sign of obstruction was found. His lower limit of 8 cm. may be well within the normal range, while the supposed upper limit of 14 cm. may perhaps be exceeded through the action of different anæsthetics on smooth muscle.

The chief value of cholangiography is in providing a permanent visual record of the medium flowing from the common duct into the duodenum. A filling defect does not necessarily indicate that a stone is present; it may also be caused by a bubble of air injected at the same time as the iodised oil. If cholangiography is done on the operating-table, this possible confusion is not important since it is a simple matter to have another look for a residual stone. If, however, cholangiography is done 10–14 days postoperatively the decision must be made whether to re-operate and again explore the common duct. If the patient develops pain when the T-tube is clamped, re-exploration is clearly essential; but if, as is usually the case, the patient is well, has no pain when the tube is clamped, and has normally coloured stools, it is doubtful whether operation is justifiable on radiographic evidence. It would be a mistake to believe that cholangiography on the operating-table will lead to the complete elimination of recurrent symptoms from a stone in the common duct after choledochostomy. Leaving a stone behind at operation is not the only cause of recurrence; for example, stones may form in the hepatic ducts and pass down into the common duct. A surgeon tells us of a case in which he found that a long tortuous cystic duct, which had been missed at the cholecystectomy, was adherent to the back of the common duct and contained a column of stones which were passing into the common bile-duct one after another.

The attraction of cholangiography during the course of the operation is that if necessary immediate action can be taken. Mallet-Guy has certainly made out a powerful case for preferring this to the more usual postoperative study.

SEEDS AND THIOURACIL

THE comparative action of drugs on animals and plants would make an interesting study; but the old intimate partnership between medicine and botany was long ago dissolved, and the average doctor's acquaintance with the effect of drugs on plants is probably confined to the occasional exhibition of aspirin to a vase of drooping flowers. A new, and better attested, example of a drug with a powerful though dissimilar action on both animals and plants has been brought to light by work on the effect of thiouracil on the germination of seeds of the higher plants. In 1949 Trotter[1] in this country and Ber[2] in Poland reported independently that low concentrations of 2-thiouracil inhibited the germination of cress seeds, and that the inhibition could be reversed by giving uracil at the same time. For effective reversal the molar concentration of uracil had to be about 20 times that of thiouracil; but uracil was more effective if given 24 hours before the thiouracil. Both workers concluded that preformed uracil must be essential to the proper germination of the seeds, and that thiouracil acted as a competitive analogue.

This work has now been confirmed and extended by Newmark,[3] of St. Louis. He found that tobacco seeds were the most convenient test-object for studying thiouracil inhibition and its reversal by uracil. A large number of chemically related compounds were tested, but only 2-thiocytosine equalled 2-thiouracil in inhibitory activity, and few others even approached it. As well as uracil, uridine and thymine reversed the inhibition.

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[7] Nelson, R. A., Mayer, M. M. *J. exp. Med.* 1949, 89, 369.

[8] Mohr, C. F., Moore, J. E., Nelson, R. A., Hill, J. H. *Amer. J. Syph.* 1950, 34, 405.

[9] Mallet-Guy, P. *Surg. Gynec. Obstet.* 1952, 94, 385.

[1] Trotter, W. R. *Nature, Lond.* 1949, 164, 63.

[2] Ber, A. *Experientia*, 1949, 5, 435.

[3] Newmark P. Paper read at 121st meeting of the American Chemical Society on April 2, 1952.

These results confirmed the suggestion that uracil (or a substance from which it is formed) is required for the synthesis of nucleoproteins in the rapidly growing plant embryo, and that this process can only be blocked by substances of very closely related structure. In animals, thiouracil does not prevent the rapid growth of tissues; it has only a highly specific action on the thyroid gland. It seems, therefore, that the mechanism by which pyrimidines are built into nucleoproteins is different in the plant and the animal. It is, however, worth recalling the occasional depression of the white-cell count by 2-thiouracil in patients with hyperthyroidism who are being treated with this drug. 2-thiouracil reduces the white-cell count more often than its methyl and propyl derivatives or other related drugs, such as 1-methyl-2-mercaptoimidazole. There is here a hint that the effect of thiouracil on the bone-marrow of susceptible people may be related to its action on plant seeds. If there is anything in this suggestion, uracil should prove an effective antidote.

Curiously enough, a parasite of the tobacco plant—the mosaic virus—is affected by thiouracil in the same way as the germinating seed. Working in the same institution as Newmark, Commoner and Mercer [4] have shown that the growth of this virus is inhibited by low concentrations of thiouracil, and that the inhibition is reversed by uracil. This observation recalls the earlier work of Strandskov and Wyss,[5] and of Wolff and Karlin,[6] who found a similar inhibition and reversal in *Bacterium coli* and *Lactobacillus casei*. Evidently a wide variety of plants require uracil, at least in the phase of rapid growth. There is a theoretical possibility that the relative insusceptibility of the animal to thiouracil could be turned to its advantage in its competition with the plant-like micro-organisms. Unfortunately one of the major enemies—the tubercle bacillus—is only slightly affected by thiouracil.[7]

Though practical developments are unlikely, it seems probable that observations on the thiouracil–uracil relationship will advance our knowledge of nucleoprotein metabolism in the plant, if not the animal, cell.

TEACHING MOTHERCRAFT

THOSE who have studied the subject say that the children in problem families are often dirty, neglected, badly fed and housed, and accustomed to squalor; but that they are seldom kept short of that primary necessity, affection. Mothers, in short, can be incompetent providers, feckless homemakers, and unreliable moral guides, without being bad mothers in their children's eyes; and when they are brought into court for neglecting those children, they are bewildered at being punished for cruelty, when they have simply been doing their best. It has long been clear that to send an incompetent mother to prison will not help her to become competent; it merely robs her children for a time of her comfortable presence. The Society of Friends intend to open a home to train such mothers in their job, and there is every hope that this—the Elizabeth Fry Home, at Spofforth, near Harrogate—will be ready by the summer. The Salvation Army have, for three years, been running the Mayflower home in Plymouth, which receives mothers who have been found guilty of neglect and put on probation. In Birmingham the city council have started a training course, in the women's prison, for women sentenced for neglecting their children. During the day the women get practical training in housewifery and mothercraft, and in the evening they attend talks given by instructors from the health, education, and child-welfare departments of the city. In Holloway, and in the Manchester prisons, the Prison Commissioners provide classes in home management. Mothers with their children may also be received in some homes on a medical recommendation.

The Lancashire Community Council, a voluntary body, are making a success of such a home—Brentwood, at Marple, in Cheshire; and this takes women convicted of neglect, as well as those recommended by doctors or social workers. An article in the *Manchester Guardian* of May 2 gives points from the case-histories of five of the ten women who were staying at Brentwood with their families during April.

A girl of 20, expecting her fourth child, lived with her husband and three children in a single room without running water. To save money for a flat she paid a woman to sit in with her children in the evenings, while she went out to work as a waitress. The sitter-in spent the money on going out to the pictures, and the mother was taken into court for neglecting her children. Another girl of 21, with two children and a husband given to selling-up the furniture, was living in two rat-ridden cellar rooms. A woman of 35 was too weak after a major operation to look after her nine children. A woman of 27, looking 16, had had five children since she left her orphanage and married a sailor. A woman of 40, looking 60, wife of a man who beat her, was nursing her seventh child—a 2-year-old—at the breast, in the hope that this would protect her from a further pregnancy.

All these women were living in circumstances which demanded qualities of character and outlook quite beyond their range. They loved their children, they were doing their best; but the odds were too heavy against them, and the ordinary remedy of society would have been to send them to prison. At Brentwood, a roomy, early 19th-century house, with a good view, standing in its own garden, they get some rest, learn some principles, and look after their own children.

Brentwood can take some thirty children under 7 as well as the ten mothers; and the average length of stay is about 6 weeks. The mothers do the laundry work and mending for themselves and their children and help the staff of eight with the housework. They look after their children, but eat apart from them, and have the opportunity, unknown in most circles today, of consigning them to nursery attendants (of whom there are four) for parts of the day. All the time they are being taught, unobtrusively, the elements of their craft—by example and suggestion rather than direction. They learn, for instance, that a floor can be scrubbed better if it is brushed first; and if this seems an elementary fact, it gives a measure of their lack of training and initiative. According to the *Manchester Guardian* report, the staff are good at being omnipresent without being officious: "Where suggestion fails they harry mildly; when it succeeds they praise."

No aftercare service has so far been possible, but the staff sometimes hear, through friends of residents, of homes better kept as a result of a visit to Brentwood a year or two before.

This home developed out of a holiday home which, between the wars, took in the families of unemployed men; during the war years it received families from the evacuated areas. It is now one of the pioneers in a new and valuable kind of social welfare, and pressure on the places available is such that cases wait nine months for admission. Yet applications to homes of this kind are only made by those magistrates or probation officers who have heard of their existence. Quite clearly we need many more such homes. At Brentwood the running costs last year were £4580. A charge of £4 weekly for a mother and £2 for each child is paid by the public-health authority or voluntary society which sends them. Plans to extend the nursery space, which at present is rather cramped, and to make room for another five mothers would cost some £15,000—a large sum to raise. Moreover, an efficient follow-up and aftercare service is needed if the work put in at Brentwood is to have full value. An experiment which has already proved its worth, and which is used by most parts of the country, certainly deserves support. The Lancashire Community Council need some far-sighted and wealthy friends.

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4. Commoner, B., Mercer, F. *Nature, Lond.* 1951, 168, 113.
5. Strandskov, F. B., Wyss, O. *J. Bact.* 1945, 50, 237.
6. Wolff, R., Karlin, R. *C.R. Soc. Biol. Paris*, 1948, 142, 87.
7. Frisk, A. R. *Acta med. scand.* 1946, 125, 487.

Special Articles

THE DANCKWERTS AWARD

A Further Step

UNDER the Danckwerts award,[1] general practitioners in he National Health Service will receive additional remunration for the years 1948–52 totalling about £27 million; nd the extra amount for 1952–53 is likely to be about 10 million. Mr. Justice Danckwerts found that, to ulfil the terms of the Spens Report, the betterment actor should be 85% for 1948–49 and 100% for 1950–51. The award also lays down that the central pool shall be djusted each year: (*a*) by reference to the number of doctors in the service, and (*b*) by reference to practice expenses.

Implementation of the award was to be conditional on: (1) a Working Party set up jointly by the Health Departments and the General Medical Services Committee reaching agreement on the distribution of the new pool; and (2) Parliamentary approval.

The terms of reference of the Working Party were as follows:

> "To secure an equitable distribution of the central pool based upon the recommendations of the Spens Committee, the object being to enable the best possible medical service to be available to the public, and to safeguard the standard of medical service by discouraging unduly large lists; at the same time, to bring about a relative improvement in the position of those practitioners least favourably placed under the present plan of distribution, to make it easier for new doctors to enter practice, and to stimulate group practice."

The Working Party has now agreed on its recommendations.

Working Party's Report

MAXIMUM SIZE OF LISTS

At present, the upper limits of practitioners' lists are:

4000 for a single-handed practitioner.

5000 for a member of a partnership, provided that the average for the partnership is not above 4000.

2400 in respect of the employment of a permanent assistant.

The Working Party has agreed that these maxima should be reduced to:

3500 for a single-handed practitioner.

4500 for a member of a partnership, provided that the average for the partnership is not above 3500.

2000 in respect of the employment of a permanent assistant.

The Working Party accepted the following principles for implementing the reduced maxima:

1. A method of remuneration would be devised which would, in general, ensure that practitioners who had to reduce their lists because of the application of the new maxima should be a little better off than they were before the award of the Adjudicator.
2. Administrative arrangements would be made to enable practitioners with lists above the new maxima to bring them within the new limits in stages over a period of time.
3. When the new limits come into full operation a practitioner would not be paid capitation fees for any patients in excess of the number permitted; but to allow a margin for changes or inaccuracies in the lists from quarter to quarter, a practitioner should be permitted a "tolerance" of up to 100 patients above the prescribed maxima and would be paid capitation fees in respect of these patients.

The reduction of the permitted maximum lists must lead to a substantial redistribution of patients both between doctors already in practice and others who may join the service either as partners of the former or who may wish to establish a single-handed practice. The redistribution of patients between doctors could only take place gradually and may not be completed for a year or more after the inception of the new arrangements.

REVISED CLASSIFICATION OF AREAS

The Medical Practices' Committee should be asked to agree new criteria for the classification of "practice areas" with the General Medical Services Committee and the Health Departments as the basis for reclassifying the country into three, instead of the present four, categories—namely, restricted areas, doubtful areas, and designated areas.

Once agreement has been reached on the criteria of classification, the Medical Practices' Committee should apply these criteria forthwith, in consultation with local executive councils and local medical committees, to the returns of the number of practitioners taking part in the service in each area as at Jan. 1, 1952. It would be open to local executive councils and local medical committees to make oral representations to the Medical Practices' Committee.

INITIAL PRACTICE ALLOWANCES

Initial practice allowances should become payable in designated areas and be paid by local executive councils. They should be a first charge on the central fund and the present system of fixed annual payments, which are a charge on local funds, should cease.

In designated areas, the following groups of practitioners should be eligible to apply for an initial practice allowance:

1. New entrants to the service who are genuinely setting up in single-handed practice.
2. Practitioners filling vacancies in small single-handed practices where the remuneration from the practice is below a specified level.
3. Practitioners who are, when the scheme comes into operation, in receipt of fixed annual payments.

To qualify for an initial practice allowance, a practitioner should have been in general practice for not less than two years or have been registered as a medical practitioner for not less than four years.

The allowance should be as follows: £600 in the first year (not subject to conditions as to gross professional remuneration or size of list); £450 in the second year; and £200 in the third year. The payments for the second and the third years should be subject to the following conditions:

1. That the practitioner has obtained 150 patients by the end of the first year; 500 patients by the end of the second year. (Provision to be made for exceptions in special circumstances at the request of the practitioner.)
2. That the payment in the second year should not be greater than the amount necessary to make up to £1000 the practitioner's gross income from professional sources during the first year. The payment in the third year should not be greater than the amount necessary to make up to £1100 the practitioner's gross income from professional sources during the second year.

The practitioner should have a right of appeal to the Minister against the decision of the executive council. In deciding these appeals, the Minister would be advised by an appeals' committee appointed by him and composed of three representatives of the Ministry of Health and three medical practitioners selected from a panel nominated by the General Medical Services Committee.

Practitioners in receipt of initial practice allowances should be paid, in addition, normal capitation fees without any deductions.

Special arrangements should be made for practitioners who fill vacancies with small lists and for other practitioners who are in receipt of fixed annual payments when the new scheme begins. The broad principles on which these arrangements would be based should be as follows:

1. A practitioner should be eligible for an initial practice allowance for a period of up to three years and no longer.
2. The maximum of three years, with the conditions related to each of those years, should, as far as possible, be applied also to practitioners who fill vacancies with small lists or who

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[1] See *Lancet*, March 29, 1952, pp. 652, 662.

make more than one attempt to set up in single-handed practice.

3. Practitioners who, when the scheme begins, have been in receipt of a fixed annual payment for less than three years should receive initial practice allowances for the appropriate balance of the three-year period, subject to the standard conditions regarding the minimum size of list to be secured at the end of each year and the maxima which are to be applied to gross remuneration.

4. Practitioners who have been in receipt of fixed annual payments for more than three years should receive an initial practice allowance of not more than £200 for one year subject to the normal maximum of £1100 gross remuneration from professional sources during the preceding year.

Exceptionally, an initial practice allowance should be payable to a practitioner now in receipt of a fixed annual payment in an area at present classified as "doubtful" or "closed" if, when the scheme comes into operation, the area is reclassified as "restricted" or "doubtful." A payment of not more than £200 should be made for one year and subject to the normal maximum of £1100 gross remuneration from professional sources during the preceding year.

A small sum of money should be set aside from the central pool to deal with cases of hardship which might arise particularly where, under the new arrangements, an elderly practitioner might lose his fixed annual payment and, after receiving an initial practice allowance for a year, find himself less well off than he was before the new scheme came into operation.

Scotland

The Scottish Medical Practices' Committee prefer to deal with individual practices as occasion arises, rather than by prior classification of areas. In Scotland, therefore, the availability of an initial practice allowance will be determined by the committee on individual application, having regard to the views of the local medical committee and executive council concerned, and in the light of general criteria framed by the committee in consultation with the General Medical Services Subcommittee (Scotland) and the Department of Health for Scotland. In addition the committee will list, from time to time, selected areas in which the need is such that initial practice allowances will be available for additional practices so long as the local conditions remain unchanged.

The detailed conditions attaching to the payment of initial practice allowances in Scotland will in other respects be the same as set out above for England and Wales, except that on account of a difference between the existing functions of the Medical Practices' Committees in the two countries it will probably be found desirable, in order to avoid a risk of conflicting jurisdiction, to entrust to the Scottish Medical Practices' Committee the determination of appeals against decisions by executive councils.

CAPITATION FEE

The Working Party has agreed on a modification of the present method of remuneration by capitation fees at a uniform rate for all patients on a practitioner's list. It has been agreed that there shall be a basic rate of payment or capitation fee for all patients, supplemented by an additional fee or "loading" for patients on a practitioner's list in excess of 500 and up to a maximum of 1000 "loadings." The details of this scheme, based on estimates of the total money in the central pool which is likely to be available for the year 1952–53, are as follows:

1. A basic capitation fee of 17*s.* per patient.

2. An additional "loading" of 10*s.* for every patient within the range of 501–1500 on a practitioner's list. (Patients added to a practitioner's list by virtue of the employment of an assistant to be paid for at the basic capitation rate and not to qualify for the loading.)

3. A final settlement, as a percentage of previous payments under (1) and (2) above. (The calculation for each year will necessarily be on a provisional basis with a later adjustment, and in order to avoid the possibility of overspending this provisional estimate will be a conservative one.)

Arrangements should be made so that the various first charges on the central pool which have, in the past, fallen on the local portions of that pool and, therefore, have contributed to variations in the capitation rate from area to area should where appropriate become first charges on the central pool itself.

Practitioners will continue to receive any monies due to them from the various first charges on the central pool, such as "mileage" and fees for treating "temporary residents," subject to any amendments in the particular schemes now in operation that may later be agreed. Apart from remuneration derived directly or indirectly from the central pool, practitioners will also, of course, be entitled to any payments due to them, for example, for maternity medical services and for any other professional services rendered by them to hospitals and other public and private bodies and to private patients.

The following table compares the gross remuneration from capitation fees under the present scheme for lists of different sizes with the corresponding remuneration under the scheme now proposed:

Size of list	Present scheme	New scheme			
	Remuneration (£) *	Remuneration (£) †	Average payment per patient	Increase in remuneration	
				£	%
500	415	425	17*s.* ‡	10	2·4
750	623	763	20*s.* 4*d.*	140	22·5
1000	830	1100	22*s.*	270	32·5
1250	1037	1438	23*s.*	401	38·7
1500	1245	1775	23*s.* 8*d.*	530	42·6
2000	1660	2200	22*s.*	540	32·5
2500	2075	2625	21*s.*	550	26·5
3000	2490	3050	20*s.* 4*d.*	560	22·5
3500	2905	3175	19*s.* 10*d.*	570	19·6
4000	3320	3475	19*s.* 10*d.*	155	4·7

* Based on capitation fee of 16*s.* 7*d* [illegible] esent the average fee paid by the [illegible] afte allowing for the elimination [illegible] ntric on doctors' lists to enable [illegible] resen and the new schemes to be calculated on the uniform assumptio that 97% of the civilian population are on doctors' lists.

† Based on capitation fee of 17*s.* plus 10*s.* for each patient betwee 501 and 1500.

‡ Excluding any initial practice allowance.

CENTRAL POOL

The utilisation of the estimated central pool for the year 1952–53 should work out approximately as follows:

	£000's	£000'
Estimated total amount in the central pool (1951–52)		50,89
Add estimate for the probable increase in number of doctors	750	75
Estimated amount of central pool (1952–53) ..		51,64
Less assumed charges on the pool other than capitation payments:		
* Mileage	1300	
Initial practice allowances	500	
Temporary residents	622	
Emergencies	5	
Anæsthetics	5	
Reserve for elderly doctors	50	
Reserve for stimulating the growth of group practices (see below)	100	
Increase in dispensing doctors' capitation fees	500	308
Net amount available for distribution as capitation fees		48,55
Estimated cost of payment of a basic capitation fee at 17*s.* per patient assuming that 97% of the civilian population are on doctors' lists ..		40,052
Net balance available for loading..		8506
Estimated cost of loading on patients on practitioners' lists between 501 and 1500 at 10*s.* per patient		812
Net balance		38

* The Working Party have assumed that, with the addition of monies from other sources, the total mileage paid will remain at £2 million.

Many of these estimates can only be very approximate, and, in particular, it is not possible to make precise estimates of how many persons will be on doctors' lists when the elimination of the out-of-date entries on these lists is completed, or of how much money may be absorbed by partnerships which take advantage of the arrangements for being paid on notional lists (see below).

Small variations in the size of the pool in future years could be dealt with by a final adjustment on a percentage basis as described in the section on the capitation fee; large variations might call for changes in the basic capitation rate or the loading.

LOADING FOR PARTNERSHIPS

In order particularly to stimulate the formation of new partnerships, including practitioners now employed as assistants and other young practitioners, arrangements should be made whereby partnerships can apply to executive councils to be paid on what the partners consider will be the financially most advantageous division of the patients between them—i.e., to be paid on notional lists. In arranging this, it will be important to devise safeguards so that only genuine partnerships of practitioners who are all in active practice can take advantage of the scheme, and so that executive councils are not asked unreasonably often to alter the basis of their patients. Consent to payment on notional lists would be subject to the review of the partnership arrangements from time to time.

GROUP PRACTICE

A sum of money should be set aside (provisionally £100,000 is shown in the table) so that it may be possible, if necessary, to introduce further measures to stimulate the formation of partnerships working as a group practice. It may, however, be found that the other measures which the Working Party has proposed will go far in this direction.

RESIDUAL PROBLEMS

The Working Party considered whether a scheme could be devised to make available from the central pool an agreed sum for distribution to practitioners by way of recognition for seniority in the service, special qualifications, and experience. The Working Party found, however, that it could not devise a scheme which would be fair and not be invidious in its application.

The Working Party is aware that the reports of two other committees considering the problems of general practice are awaited—the British Medical Association's general practice review committee and the Central Health Services Council's committee on general practice. The reports of these two committees may indicate other ways of improving the organisation of general practice.

Observations by the General Medical Services Committee

The Working Party's report will be considered by a special conference of representatives of local medical committees on June 26; and in its report to that conference the General Medical Services Committee expresses the belief "that general practitioners will acclaim the Danckwerts Award as a fair and just determination of the size of the central pool."

BETTERMENT FACTOR

The committee says that the Minister of Health has declared that he cannot accept the committee's contention that the award involves the principle of a varying betterment factor to be applied to future years. In discussions with the Ministry it became clear that the Government was unwilling to "insulate" the profession for all time against fluctuations in the cost of living. "In view of the national situation, the Committee is of the opinion that it should not press for a further increase in the betterment factor for the years 1951-52-53."

ARREARS OF PAY

The committee has received from the Ministry detailed calculations which show that the arrears due to the profession for the four years 1948-52 amount to £26·948 million, made up as follows:

Year	Amount (£s million)
1948-49	4·054
1949-50	4·554
1950-51	8·883
1951-52	9·457
	26·948

It is intended that these arrears should be paid to every general-practitioner principal in the National Health Service (or, if deceased, to his legal representative) whose name has been included in a medical list for the provision of general medical services and who has received payment from the central pool for any period since the appointed day. Payments of arrears will be related solely to previous payments from the central pool apart from mileage.

There is evidence, says the committee, that the total mileage fund over the past four years has been adequate for its purpose, and no retrospective adjustment will be made for mileage payments. Other payments—e.g., for maternity medical services—which do not come out of the central pool will not attract back payments.

The Board of Inland Revenue has agreed to discuss with the committee the problem of income-tax and sur-tax on back payments.

Clearly, the committee continues, only N.H.S. principals are legally entitled, as a right, to a share of the arrears of payment. Assistants and salaried partners are not covered by the award.

"The committee holds the view that, in discharging its duty to the profession in negotiating the distribution of back payments, it would be wrong to depart from the legal implications of the Award. It can therefore make no recommendation on the matter, but believes it right that any retrospective adjustment of assistants' salaries should be left for consideration by individual principals."

DATES OF PAYMENTS

The recommendations of the Working Party, when approved or modified by the special conference on June 26, will be referred to the Minister. It is understood that the Minister will inform Parliament of the Working Party's findings at or before the time when the Supplementary Estimate is submitted in July. Assuming that the Supplementary Estimate is approved in July, it should be possible to start paying the arrears before the end of this year.

A good deal of preparatory work will, says the committee, be necessary before the new scheme of distribution recommended by the Working Party can be put into effect.

Firstly, it is important that the clearance of doctors' lists should, as far as possible, be completed. Secondly, individual doctors will need to be advised in advance of the precise details of the scheme, and those in or contemplating partnership must be given time to decide the financially most advantageous division of the patients in the practice. Thirdly, that part of the scheme relating to initial practice allowances cannot be fully implemented until the Medical Practices Committee has been able to reclassify the country for the purpose of designating areas which will attract these allowances.

"It is therefore not yet clear whether because of the heavy preparatory work required the new distribution scheme can be brought into effect by the first quarter of the new calendar year or the first quarter of the new financial year."

". . . To-day the man-in-the-street is the patron of science. Without his support our universities and research institutions could not pay even their salary cheques for the next quarter. Therefore the interpretation of science to the public has now become a major activity in modern society, not to be entrusted entirely to the efforts of scientific journals; and the British Association remains the chief instrument for this activity."—ERIC ASHBY, D.SC. *Nature, Lond.* May 17, 1952, p. 813.

GENERAL MEDICAL COUNCIL

SESSION MAY 27–30

OPENING the 184th session of the General Medical Council on May 27, Prof. DAVID CAMPBELL, the president, observed that the council welcomed the Bill now before Parliament to transfer to a General Dental Council the G.M.C.'s duties in relation to dental education and discipline. In 1948 the dental executive committee began to review the dental curriculum. The committee's recommendations, which were the counterpart in the field of dental education of the council's recommendations on the medical curriculum, superseded those adopted in 1933. They specified a number of new subjects, but the minimum length of professional study remained unchanged at four years. "The recommendations are in no sense an attempt to impose on bodies and schools either a uniform curriculum or stereotyped methods of teaching."

Turning to the Medical Act of 1950, the President said that the Republic of Ireland had adopted a parallel measure in the Medical Practitioners Act of 1951. Essentially this was the same as the British Act, but there were two important differences:

1. Under the Irish Act hospitals and resident posts for Irish graduates and diplomates would be approved, not by individual licensing bodies as in this country, but by the Medical Registration Council of Ireland. This provision was in harmony with section 7 of the 1950 Act, which provided for the exercise of such powers by the Medical Registration Council in relation to holders of diplomas granted in the Republic of Ireland.

2. The Irish graduate would have the right to provisional registration as soon as he qualified, whereas in this country an applicant for provisional registration must not only have qualified but must also have been selected for a resident post.

The President understood that the Irish authorities would be prepared to introduce the compulsory period of residence as a condition of full registration in Ireland at the same time that this step was taken in Britain.

In conclusion the President referred to reciprocal registration between Britain and the Commonwealth countries:

> "Like many of my predecessors in office, I have always been a wholehearted supporter of reciprocal rights of registration between this country and others owing a common allegiance. I regret, therefore, that there are still some Provinces of the great Dominion of Canada with which we have no reciprocal relations. I fully realise the reason for this. There does not appear to be on their part any disinclination to recognise British qualifications as such; but some of the Provinces, and indeed certain of the other Dominions, in view of their self-governing powers, desire to have a say in the recognition of other qualifications, and are reluctant to admit, in virtue only of their British registration, practitioners whom they do not desire to see largely represented within their borders."

The pathway to the solution of this difficulty was, however, still open, and indeed had been made easier by the provisions of the Medical Act of 1950.

ROUTINE BUSINESS

Dr. J. P. HEDLEY, senior treasurer, presented the report of the finance committee for 1951, which showed an excess of income over expenditure of £4267, and an increase in the assets of the three branch councils.

The council received the annual examination returns. Dr. A. W. M. ELLIS thought it would be helpful to have a figure for rejections in the whole of the final examination. Prof. R. M. F. PICKEN remarked that it would be difficult to supply this information where, as in the University of Wales at the present time, the examination could be taken in parts. It was decided to ask for the information where it could be obtained. On the returns of examinations for certificates and diplomas in public health, Sir ANDREW DAVIDSON wondered whether the majority of those who obtained the certificate went on to take the diploma. If so, this would vitiate the value of the certificate, the idea of which was to give a background in public health to people like chest physicians and venereal-disease experts. Professor PICKEN said that in Wales most of those who took the certificate did not go on to the diploma. The council decided to ask the licensing bodies for figures on this point.

Dr. H. GUY DAIN, presenting the report of the Pharmacopœia Committee, remarked that the *British Pharmacopœia* continued to be a "best seller"—so far 47,419 copies had been sold. The *Addendum, 1951*, had sold 12,083 copies. The committee had adopted the draft of the *British Pharmacopœia, 1953*. Dr. Dain said that this seemed likely to be ready early next year—in March or April. The date of implementation would be six months after the date of publication.

Sir SYDNEY SMITH was re-elected chairman of business.

The council met in camera to discuss certain matters.

DISCIPLINARY CASES

The council considered two disciplinary cases in which judgment had been postponed.

Joseph Kevin Conlan, M.B. Durh. (1940), registered as of 81, Stubbington Avenue, North End, Portsmouth, on whom judgment had been postponed for two years after he had been found to have been convicted of charges of obtaining money by false pretence, appeared and presented a testimonial. The registrar was not directed to erase his name.

The council noted with satisfaction the testimonials produced by *Garden Hepburn Swapp*, M.B. Aberd. (1928), who had convictions for driving a car whilst under the influence of drink, and awaited his further appearance in May, 1953, judgment having been postponed in November, 1951, until that session.

Medical Disciplinary Committee

The Medical Disciplinary Committee began its sitting on May 28, under the chairmanship of Professor Campbell.

APPLICATIONS FOR RESTORATION

Ram Kissoon Nandlal, whose name had been removed from the Register in March, 1951, after he had been found guilty of infamous conduct in having intercourse with a married woman who was a patient, applied for restoration. The committee did not direct the registrar to restore the name of Ram Kissoon Nandlal.

Gurdit Singh Malik applied for the restoration of his name. It was removed in May, 1951, after he had been found to have given a yellow-fever certificate when he had not inoculated the patient. A cable from the director-general of health services in India (who laid the original complaint) suggested that the committee might consider restoring Dr. Malik's name. Mr. N. Leigh Taylor said that Dr. Malik's name had not been erased from the Punjab register, and he had continued practice in Delhi. This enabled him to show that it had been an isolated lapse. Mr. Taylor referred to a letter from the hon. secretary of the Indian Medical Association. The committee directed the registrar to restore to the Register the name of Gurdit Singh Malik.

POSTPONED CASES

The committee considered three cases on which judgment had been postponed.

John Vincent Gill, M.B. Belf. (1944), registered as of 62, May Street, Belfast, who had convictions for driving a car while under the influence of drink, attended and produced six testimonials. The registrar was not directed to erase his name.

James William Hay, M.B. Aberd. (1924), registered as of 51, Spencer Street, Carlisle, who had convictions for driving a car while under the influence of drink, was not present but was represented by Mr. T. Strong, solicitor. Mr. Winterbotham, solicitor to the council, called a witness who said that when she visited Dr. Hay in his surgery last May he seemed to be under the influence of drink. Mr. Strong read a letter from Dr. Hay saying that he had suffered from colic, and that he did not recollect this patient nor taking any alcohol that day. This was the first time that any patient had implied negligence, and his practice remained at the high figure of 3000 patients. The committee further postponed judgment until November.

Harold Stanley Groves, M.R.C.S. (1915), registered as of The Poplars, Blagreaves Lane, Littleover, Derby, who had been convicted of driving under the influence of drugs and drink, was represented by his wife, who said he had not been practising for two years. The registrar was not directed to erase his name.

NEW CASES

ALLEGED INFAMOUS CONDUCT

Jeremiah Joseph O'Sullivan, M.B. N.U.I. (1947), was charged with infamous conduct in a professional respect in that he had, at Fogo, Newfoundland, conspired to procure the miscarriage of a woman, and by a letter unlawfully incited another doctor to procure the miscarriage. Mr. N. Leigh Taylor, of Messrs. Hempsons, appearing in his personal capacity, said that no abortion was performed. The registrar was directed to erase from the Register the name of Jeremiah Joseph O'Sullivan. This is subject to appeal to the Privy Council within 28 days.

ALLEGED MISUSE OF FORMS

John Howard Crawford, M.B. Leeds (1934), registered as of 16A, Wimborne Road, Bournemouth, was charged with submitting E.C.19 forms purporting to relate to 19 persons, for which he received the sum of 15*s.* in each case from Bournemouth Executive Council "whereas, as you well knew, you were in the circumstances not entitled to such sum." Mr. Howard said that between July and September, 1950, Dr. Crawford submitted 247 E.C.19 forms and was paid 15*s.* in respect of each. 19 of them were picked out, and the names of these so-called temporary patients were the ones set out in the schedule to the charge. It was alleged that the doctor sent in these forms which purported to bear the signature of the patient, whereas in fact they had not been signed by the patients and he knew that none of the patients had applied to come to him as temporary patients; nor had he given them treatment, except in one case, where he had treated the boy before the period covered.

Mr. R. Willoughby Lowe, clerk to the council, gave evidence. In cross-examination by Mr. N. Leigh Taylor on behalf of the Medical Defence Union, Mr. Low said that the local medical services committee, which investigated the matter, had ordered a reduction of £250 from the doctor's remuneration; an amendment that the amount should be £150 was defeated; the Minister had approved the reduction of £250.

The committee found proved the facts alleged in the charge. After consideration in camera the Chairman told Dr. Crawford that the committee regarded with grave concern the facts of the charge. They were unable to regard the statement made on his behalf as a justification; but, having regard to the assurance which he had given as to his future conduct, they would postpone judgment for one year until May, 1953.

CERTIFICATION

Edward Boyd, M.B. Belf. (1942), registered as of 9, Madrid Street, Belfast, was charged with having given three certificates for sickness benefit stating that he had examined Patrick Eccles when he had not in fact examined him on those dates, these certificates being untrue, misleading, or improper within the meaning of paragraph 1 of the Warning Notice. Dr. Boyd appeared but was not represented. After consideration in camera, the Chairman announced that the committee had not found the facts alleged proved to their satisfaction, and therefore found the doctor not guilty of infamous conduct in a professional respect.

UNLAWFUL KILLING

The committee considered the case of *Sumatapalage Reginald Gunewardene*, L.M.S.S.A. Lond. (1942), registered as of 53, East Dulwich Road, London, S.E.22, who was charged with having been convicted at the Central Criminal Court in March, 1951, of unlawfully killing Grace McLean, when he was sentenced to three years' imprisonment. Mr. Winterbotham, presenting the facts, said that the woman died of gas-gangrene infection due to septic abortion, but Dr. Gunewardene did not perform the abortion himself. He had obtained a remission and was now free. The registrar was directed to remove from the register the name of Sumatapalage Reginald Gunewardene. This is subject to appeal to the Privy Council within 28 days.

CHARGES OF DRUNKENNESS

Thomas Joseph Doran, L.A.H. Dubl. (1942), registered as of 42, Upper O'Connell Street, Dublin, was charged with infamous conduct in a professional respect in that he had, on Jan. 4, 1952, called on a patient in Liverpool when so far under the influence of drink that he was unfit to attend or treat her. The Chairman announced that the committee found that the facts alleged were not proved, and that Dr. Doran was not guilty of infamous conduct in a professional respect.

Alan McKerlie, M.B. Aberd. (1937), registered as of Upper Chorlton Road, Manchester 16, was charged with having been convicted on Jan. 2, 1951, at the City of Manchester magistrates' court, of being drunk and disorderly, when he was fined 20*s.*; of having on Aug. 3, 1951, driven a motor-car when under the influence of drink, when he was fined £25 and disqualified from holding or obtaining a driving licence for twelve months; and of having been fined 20*s.* and ordered to pay £5 5*s.* costs for unlawfully assaulting Susan Hopkins. The committee postponed judgment for one year until their session in May, 1953.

Thomas Patrick Smyth, L.A.H. Dubl. (1939), registered as of 32, Market Street, Atherton, Manchester, was charged with convictions in 1948 and 1951 of driving a motor-car whilst under the influence of drink. He had been fined £10 and £3 3*s.* costs and £100 and £2 2*s.* costs respectively, and on both occasions was disqualified. Judgment was postponed for one year.

Parliament

Health Service Charges

IN the House of Commons on May 28 Dr. BARNETT STROSS presented a petition signed by 211,577 British subjects asking the House to alleviate the distress arising from the new charges on prescriptions, on dental treatment, and on surgical appliances in the National Health Service.

The Opposition has tabled prayers for the annulment of each of the eight orders laid before Parliament providing for the new charges to come into force on June 1. The orders remain open to challenge for 40 sitting days. The prayers cannot be debated until after Parliament reassembles on June 10.

QUESTION TIME

Cancer Cure Claim

Mr. PETER FREEMAN asked the Minister of Health whether he was now in a position to make a statement on the results of the inquiry into the Rees Evans cancer cure.—Mr. IAIN MACLEOD replied: A committee was appointed by my predecessor in October, 1950, consisting of Sir Robert Robinson, as chairman, Sir Ernest Rock Carling, Sir Alexander Fleming, and Sir Harold Himsworth, to consider the claims made by Mr. Rees Evans to have discovered a treatment for cancer, and to advise whether they warranted further investigation and if so the way in which any investigation should proceed. The report has now been received, and in the normal way I should have proposed to publish it; but as it contains information supplied to the committee in confidence by Mr. Rees Evans and by patients and their relatives, I cannot do so. I can, however, say that the committee have advised me that the claims made do not warrant further investigation, and I have accepted that advice.

The following fuller statement of the committee's conclusions was circulated in the Official Report.

> The committee examined the histories of British and American patients treated by Mr. Rees Evans, and also investigated the materials used by him in his work, as well as receiving oral and written evidence from him. They did not examine patients under treatment, since it considered that, in most forms of cancer, assessment of the results of treatment is not possible until the patient has remained well for at least five years after treatment has ended, and also since the technical details of applying any particular treatment are irrelevant to the assessment of its value in treating cancer.

Examination of the histories of 22 British patients treated by Mr. Rees Evans between 1931 and 1945 who could be traced from 34 names supplie[illegible] the following conclusions:

Insufficient [illegible]	5
Judged not [illegible] [illegible]icer	7
No convincing evidence of cancer at time of treatment	3
Dead from or seriously ill from recurrence of cancer after treatment	2
Rodent ulcer	5

Inquiries were not pursued in the cases of rodent ulcer on the grounds that it is a form of skin cancer of slight malignancy; that it has been known for many decades that it can be successfully treated by several methods which remove the locally affected tissue; and that evidence of success in healing rodent ulcers throws no light on whether the same method will be useful in the treatment of cancers in general.

Examination of the histories of 16 American cases treated by Mr. Rees Evans in 1949–50 was also made, and the condition of these patients in July, 1951, was as follows:

Dead from cancer	8
Seriously ill from cancer	1
No convincing evidence of cancer	2
Condition doubtful	1
No recurrence of cancer, but also treated surgically or with X rays	2
Rodent ulcer	2

On their inquiries into these British and American cases the committee came to the conclusion that they provided no evidence that the Rees Evans treatment of cancer is of any value, though it may have an effect on rodent ulcers. Samples of the materials used by Mr. Rees Evans in treatment were analysed, and tested in experiments on animals. The committee were advised by a leading expert that the results obtained did not provide any indication for recommending further experiments.

Bone-conduction Hearing-aids

In answer to a question Mr. MACLEOD said large-scale trials into bone-conduction hearing-aids, under the auspices primarily of the Medical Research Council, had been going on for some time, and were within a matter of weeks of completion. It was expected that the results would be issued by the end of July and after that he hoped to be able to go ahead with the production of this aid. Almost exactly 4000 patients were awaiting this type of aid.

Boards and Committees

Mr. J. A. SPARKS asked the Minister what changes he proposed to make in the functions and responsibilities of regional hospital boards and hospital management committees.—Mr. MACLEOD replied: I do not propose to make any changes at present.

Mr. SPARKS: Is the Minister aware of the recommendations in the report of the Select Committee on Estimates? Is he now saying that he proposes to take no notice of them? Mr. MACLEOD: No, Sir. The report has already been acted upon. The power to approve hospital management committees' estimates and to permit transfers between-subheads has already been restored to regional boards as a result of the report. Mr. SPARKS: Is the Member satisfied with the arrangement as it now exists? Mr. MACLEOD: I should not say that I am fully satisfied. I am satisfied that the point made by the Select Committee has been met, but this is, of course, one of the biggest problems in the National Health Service, and I am looking at it all the time.

Supplies of Cortisone

Mr. CLEDWYN HUGHES asked the Minister if he was now in a position to state whether the experiments into the use of the drug cortisone had been completed; and when the drug was likely to be available for the treatment of arthritis and allied ailments through the National Health Service.—Mr. MACLEOD replied: A fair appraisal of the value of cortisone will require much longer trial than has yet been possible. The number of special centres at which the drug is provided under the National Health Service has been increased recently from 55 to 70, and supplies have been made available to other hospitals for treatment of certain eye conditions.

National Insurance Medical Certificates

Mr. C. J. SIMMONS asked the Minister of National Insurance if he would arrange for his local offices to issue, free of charge, duplicates of the free medical certificate supplied to National Health Service patients when these were necessary to enable patients to secure payment of benefits from friendly societies or sick-clubs.—Mr. R. H. TURTON replied: Extracts of National Insurance medical certificates are already supplied, free of charge, at the request of a claimant to any registered friendly society or trade union of which he is a member. The Minister would not feel justified in extending this arrangement.

In England Now

A Running Commentary by Peripatetic Correspondents

THOSE readers who have been troubled by our inability to obtain a bat should take heart; matters are now in train. We did what we should have done at first, and approached our Animal Man. Animal Man, we said (rather diffidently, for we rarely penetrate so far into the animal-house); we are anxious to secure a bat. Yes, sir, he said, laying down his copy of Stephen Potter (he is an advanced Lifeman), what species had you in mind? But we were ready for him. Oh, we said airily, either a Vespertilionid or a Rhinolophid—it's really immaterial. He took it well. Within ten minutes we had learnt both the sporting and unsporting methods of shooting bats, how to bring them to the ground with a long bamboo cane, and the correct technique of trapping them in an old felt hat advanced stealthily over their sleeping bodies. Within half an hour we had ruled out the local church towers because of the swift census. (How's that again? we inquired. Because of the census of swifts, he said pityingly.) Within an hour we had arranged an excursion to a church he knew of where the vicar was Troubled with Bats. Indeed, the ecclesiastical authorities had taken the desperate step of placing in the belfry two stuffed owls to arouse doubts in the minds of the bats. There they still were, said the Animal Man, and uncommonly sheepish they look, if such a term can be applied to stuffed owls.

Our excursion is not until next week, but we have no doubt of the outcome; it would be a bold bat who would take the responsibility of evading our Animal Man.

* * *

The Zoologist in the Above Case writes:

"I fear that I cannot supply green lizards bred in the rural wildernesses of England. Also the colour of my lizards requires a more accurate description; for although they are surrounded by the rural splendours of Oxfordshire, I can only catch them in quantity in the habitat which they evidently prefer to these splendours—my coal-bunker."

* * *

It was a Consultation that took me through the chinks in the Yugoslav iron curtain; but these have lately been opened for a tourist drive, and in the beautiful Italianate towns of the Dalmatian coast Communism is veiled. Sunshine, flowers, the great Dinaric Alps coming down to the sea, their lower slopes terraced in vineyards, a nightingale singing over a rocky cove where one plunged into translucent water—all these divert one from the empty harbours, the inland villages gutted and roofless, and the plain fare and hard beds provided at the hotels. It is an Alice in Wonderland world. "There is no coffee—will you have tea?" "Yes, please." "And rum?" "Yes, please." (We had tasted the sweet pale water known as tea.) "There is NO rum." Babel prevails: a few words of German, Italian, French, and even English are spoken, but the reply is rarely understood. We painfully acquired a few phrases of Serbo-croat, a Slav language with an impossible grammar and Cyrilic alphabet, wherewith to ask about transport and times. This effort proved quite useless, for the answer never corresponded with the event; as a Yugoslav lady, a fellow strandee, observed: "*Informations* are so difficult."

The patient was an ecclesiastic in remote Montenegro, and we came into an atmosphere of fear and apprehension. We ourselves were under the direct and suspicious surveillance of the police, who summoned us before them and delayed our departure by a day. The courteous and helpful Serbian becomes hard-faced when put into uniform. It is very sad.

Our arrival was, I suppose, typical, but disturbing to the punctual Western mind. The ship having "broken down"—a common phrase—we took to the stony narrow road along the side of the mountains, with overhanging cliffs on one side and an abyss on the other. The "autobus" was explosive and uncertain, stopping for indefinite periods at villages in the valleys; but it negotiated the steep climbs and crashing hairpin descents, and even recovered after petering out on a high shoulder.

We were finally decanted in the dark outside a large, lonely house, set among rocks, orchards, and vineyards.

The next day was given to Medicine. We spent the morning examining our patient, and tried to convince him that his main trouble was overdosage of digitalis. In the afternoon after waiting about for two hours, we were fetched by the ambulance to inspect the hospital of Stari Bar, the old Turkish hill town crowned with impressive ruins and surrounded by olives. The streets are narrow, cobbled, and stepped, impossible for wheeled traffic; oxen plough under the olives; donkeys and women seem interchangeable beasts of burden—yet the autobus climbs each day to a plateau nearby and the radio blares propaganda and jazz music from the café. The hospital, a white modern stone building, lies at the foot of the hill; it is well planned and equipped entirely by America to a standard above many of our own smaller hospitals. There are 50 beds, a small X-ray plant, and a good theatre with an up-to-date table and the newest gadgets. The wards are airy with ample spacing, about 10 beds to a ward; for medicine, surgery, septic cases, gynæcology, and midwifery; the antenatal ladies were grouped round the door in peasant dress and Turkish trousers. Apart from this pleasant feature we were in a familiar world.

The medical staff consists of a keen young Yugoslav surgeon, his wife, and two housemen who said modestly that they had been qualified for only six months. No consultant physician is available, though a surgeon can be summoned from Belgrade; blood for transfusion also comes from Belgrade, so far by air and then by the autobus or ambulance; we saw a man who had survived transfusion with this well-shaken blood.

My advice was sought on several medical cases and given firmly on insufficient evidence, and my surgical colleague was eagerly questioned about such things as the merits of vagotomy. Sometimes an animated discussion foundered in an acute shortage of German. The patients understood nothing, but had probably been told of our visit; at any rate the appealing eyes of a young woman with heart-failure and ascites prompted two halting words to indicate a hopeful prognosis. The grateful relief in those eyes was a high reward.

Although the hospital is a government institution and therefore anti-religious, we were invited into the chapel maintained for the nursing sisters. We observed that the doctors stayed outside, and we all partook of a collation in what was virtually the anteroom of the chapel.

Our mission ended, it was no easy matter to depart; but, having satisfied the police and torn ourselves from our patient, we waited hopefully in the road from 5 A.M. Five days of travelling by bus, boat, and train ensued; emergencies arose; plans were changed; we came near arrest; we were left behind; we waited for hours in a wood to leap into the Simplon Orient Express; and finally we crossed the Channel on the day intended.

* * *

Christopher and John were playing hospitals. Grannie was stretched out on the sofa for them to bandage her ankles, one leg each. John's bandaging had become rather disorientated, and he was poaching on Christopher's reserves. Chris was indignant: "No, John," he cried at last, "you're only a doctor for *left* feet." Is this a foretaste of the future ultraspecialised surgery?

* * *

The Scottish thistle will no longer be alone in its proud boast, "*Nemo me impune lacessit,*" if a new range of agricultural insecticides comes into general use among vegetables. These chemicals, known as "systemics," contain phosphorus and owe their discovery to research done on neurotoxic gases in the late war. Taken up by the plant from the soil they circulate in its sap, and they are lethal to winged or crawling parasites that feed on the roots or foliage but harmless to the friendly insects that visit the plant merely for purposes of pollination. They are also harmless to man, so Smith minor will not get any scientific evidence here to support his aversion to spinach.

* * *

News from School.—"The School photograph has come out, and almost everyone looks terrible."

Letters to the Editor

SURGERY OF PEPTIC ULCER

SIR,—I am glad that Sir Heneage Ogilvie (May 31) has brought to bear the weight of his authority and experience and his gift of words against the removal of peptic ulcers in their active phase. Perhaps he does not go far enough even, in that he mentions two-stage operations[1] for actively inflamed œdematous ulcers, the inactivated ulcer being removed at a second operation. For whereas surgical experience confirms all too frequently the inadequacy of present medical treatment as a definitive treatment for chronic peptic ulcer, medical treatment is almost uniformly successful in temporarily converting an active ulcer into an inactive one. For some years now we have as a routine been preparing peptic ulcer cases for operation by a preoperative milk drip for one to two weeks and sometimes longer. Cases with pyloric stenosis, which will not tolerate a milk drip, are prepared by frequent small milk feeds and gastric lavage. We have had only one case in which an active ulcer was not rendered inactive before operation. The advantages to the patient and the technical ease for the surgeon of operating in the inactive phase are such that the increased time of occupation of a surgical bed before operation is more than justified, and is in fact in part saved by the quicker and smoother post-operative course of many cases.

London, W.1. DAVID H. PATEY.

SIMPLE TEST FOR BLOOD-A.C.T.H.

SIR,—In earlier communications[1, 2] I described the chromatophorotropic effect of A.C.T.H. This work has been independently confirmed by Johnsson and Högberg.[3] The chromatophorotropic effect of A.C.T.H. has not so far been separated from its other effects despite a variety of chemical and other procedures,[1] and seems related in some way to the pigmentation of the skin in man which becomes evident in the following three conditions: (1) A.C.T.H. administered in large doses, (2) A.C.T.H. overproduction in pituitary Cushing's disease; and (3) Addison's disease with increased A.C.T.H. output as a compensatory mechanism.

I have developed a simple and sensitive test-object which gives a specific reaction to chromatophorotropic activity and allows easy determination of A.C.T.H. in blood for clinical purposes.

It remains to be seen whether chromatophorotropic activity is a separate hormone factor or simply an A.C.T.H. fraction of low molecular weight. So far I have the impression that chromatophorotropic activity in man parallels the total A.C.T.H. output, because in normal blood such activity roughly corresponds to that described for the adrenal ascorbic-acid-depleting activity.[4, 5]

Test Animal

The tree-frog *Hyla arborea* is a reliable test animal; it is available in many laboratories because of its use in pregnancy tests,[6] but any green rana species may be used. When kept for one week in captivity on a white table, tree frogs assume a uniform bright-green colour (stage of adaptation). After one week the frogs are kept for one day on a brown table. If they remain green, they are ready for use (stage of challenge). The test itself is carried out on a white or green table in order to prevent "false positives." When injected with A.C.T.H. the green-adapted frogs assume a dark olive colour within 15–30 minutes (after excessive doses they become dark brown within 2–4 hours). Three frogs are used for one A.C.T.H. concentrate from human blood. They are injected with a 22-gauge needle which is introduced from

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1. Sulman, F. G. *Ref. Veterinarith*, 1952, 9, 31.
2. Sulman, F. G. *Nature, Lond.* 1952, 169, 588.
3. Johnsson, S., Högberg, B. *Ibid*, p. 286.
4. Cooke, A. S., Graetzer, E., Reiss, N. *Endocrinology*, 1948, 5, 89.
5. Bornstein, J., Trewhella, P. *Lancet*, 1951, ii, 678.
6. Bromberg, Y. M., Brzezinski, A., Rozin, S., Sulman, F. G. *Acta endocrinol.* 1951, 7, 31.

the hindleg through the gluteus region into the dorsal lymph-sac or into the ventral subcutis. This technique avoids any leakage. A neutral pH of the fluids to be injected is essential and it should be adjusted carefully in order to prevent toxic effects.

Concentration of A.C.T.H. from Blood

1. 20 ml. of blood withdrawn from the cubital vein is immediately transferred to a bottle containing 20 ml. of distilled acetone and 0·5% glacial acetic acid. This procedure inactivates any A.C.T.H.-decomposing enzyme of the blood and precipitates inert proteins.

2. The suspension is sucked through a 1–2 in. Buchner funnel with Whatman filter-paper no. 1, and the precipitate is washed with 5 ml. of 50% acetone. The pooled filtrates (approximately 25 ml.) contain the whole A.C.T.H.

3. This filtrate is carried over to a 100 ml. bottle, and 60 ml. of distilled acetone is added, which precipitates A.C.T.H. within an hour. In order to facilitate precipitation and sedimentation, 10 ml. of ether is added immediately and the bottle is allowed to stand overnight in the refrigerator.

4. Next morning the supernatant fluid is decanted; the precipitate is washed with about 5 ml. of ether, the ether decanted, and the residue freed from traces of ether by standing for about 30 minutes.

5. The A.C.T.H. precipitate is dissolved quantitatively in 0·8 ml. of $N/20$ NaOH with the addition of 1–2 drops of a standard bromthymol-blue indicator solution. If the precipitate does not completely dissolve, the bottle should be shaken in a shaking apparatus. Finally, some drops of $N/4$ acetic acid are added until the solution becomes green, avoiding, however, iso-electric precipitation.

6. The concentrated A.C.T.H. solution (approximately 1 ml.) is injected into green-adapted tree frogs as follows:

Frog 1.—0·1 ml. (i.e., 2 ml. of blood corresponding to 500 frog units per litre blood).
Frog 2.—0·3 ml. (i.e., 6 ml. of blood corresponding to 166 frog units per litre blood).
Frog 3.—0·6 ml. (i.e., 12 ml. of blood corresponding to 83 frog units per litre blood).

It is difficult to correlate the frog unit with the international unit. With the international standard preparation of A.C.T.H. 1 µg. is equivalent to 1 frog unit. This correlation is, however, not necessarily directly applicable to other preparations.[7]

The above simple method enables the A.C.T.H. content of blood to be determined within 12 hours. I feel that this assay is as easily carried out as an Aschheim-Zondek test. It is of obvious use in the differential diagnosis between pituitary Cushing syndrome and adrenal Cushing syndrome.

ology,
Hebrew Medical School, F. G. SULMAN.

AN ILLUMINATED SUCKER TUBE

SIR,—The sucker tube which Mr. Everidge illustrates in your issue of May 3 is very similar to the one I have been using for some time.

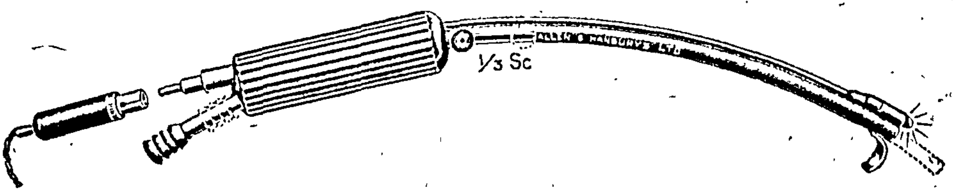
I believe that my instrument has some advantages over that of Mr. Everidge. For instance, I have had a short retractor welded to the sucker (see figure). With the retraction of the tissues that is thus possible the sucker and light can be got down more readily to the source of bleeding. Thus in either a transvesical or retropubic prostatectomy the capsule of the prostatic cavity can be retracted, and the sucker and light applied direct to the bleeding-point without any obstruction to vision.

In addition, the sucker tube can be advanced or retracted at will by means of a small knob on the shaft of the instrument. This again is an advantage, because it prevents the bulb of the light being coated with a film of blood, so obscuring the field of vision. The sucker-light retractor is curved so that it does not obscure the field from the operator.

This instrument has been a great boon to me in doing prostatectomies, as it enables me to see exactly where the bleeding is taking place. It also has advantages in many other operative fields, such as thyroidectomy (in retracting the infrahyoid muscles), cholecystectomy (if hæmorrhage occurs deep down in the wound), and in othe operations where suction, light, and retraction are neede simultaneously. It does away with a multiplicity c instruments deep down in a wound.

I am indebted to Messrs. Allen & Hanburys Ltd., wh coöperated with me in evolving this sucker-light retractor.

London, W.1. MAURICE LEE.



COTTON SUTURES

SIR,—In your leading article of March 1 you refer t possible economies in the hospital service. One possibl economy is to use cotton sutures.

Chiefly for the sake of economy, we use at this hospita ordinary sewing cotton, of grades 40 and 60, for almos every type of suture, including peritoneum, muscle sheaths, ligatures, and skin. We use catgut only i vaginal and perineal repairs, and in operations fo hæmorrhoids and on the bowel mucosa. If properl sterilised by boiling or autoclaving these non-absorbabl sutures are innocuous and in many ways superior t catgut; for example, in old people with poor tissu reaction one knows that there is no danger of the woun breaking down as there is after catgut has been absorbed

Since being introduced to cotton sutures four year ago, by Dr. R. A. Hughes, of Shillong, I have seen no a single instance of wound sepsis or malunion in a varie series of major and minor cases.

Christian Mission Hospital,
Rajshahi, Pakistan.
I. T. PATRICK
Medical Superintendent.

POSTURAL NERVE BLOCK FOR INTRANASAL OPERATIONS

SIR,—I was interested to read the article by Dr. Curtis in your issue of May 17. I have myself used Moffett' instillation method of local analgesia with good results The modification suggested by Dr. Curtiss also seem satisfactory.

It would appear, however, that there is always risk that the patient may swallow some of the cocain solution. Perhaps a safer method is to use a 25% cocain paste made up as follows:

Cocaine hydrochloride	2 drachms
Desiccated adrenal gland (5 in 1) ..	gr. 24
Chlorbutol	gr. 5
Liquid paraffin	220 minims
Soft paraffin	to 1 oz.

This is smeared on to a cotton-wool applicator, which i applied directly to the region of the sphenopalatine ganglion The ganglion is immediately behind the posterior end of th middle turbinate bone. Positioning of the applicator is no difficult, and need only be approximate.

Two further cotton-wool-mounted applicators are required one is directed to the roof of the nose to block impulse along the anterior ethmoidal nerve, and the other is place along the inferior meatus of the nose to catch the nasa branches of the anterior and posterior superior dental nerves

Preliminary light spraying with a weak solution of cocain renders the introduction of these applicators painless, an with reasonable care there is no trauma to the mucosa

The big advantage of usin paste is that absorption i virtually only local. Cocain is not ingested, and s intoxication is rare. Another advantage is that the procedures can all be carried out in the ward before th patient is brought down t

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7. Sulman, F. G. *Endocrinology* (in the press).

e operating-theatre. Even if the start of the operation is nduly delayed the cocaine continues to act and analgesia still complete. With the instillation method, the patient presumably brought down to the theatre block some time efore the operation is to take place. This may cause overrowding, apart from the possible unpleasant psychological fects on the patient himself.

The method I describe is used successfully in several entres. Mr. Myles Formby first taught me the echnique.

Oldham Royal Infirmary. NORMAN APPLETON.

RELIEF OF PAIN IN LABOUR

SIR,—It is gratifying to read the letter in your issue of ay 17 telling us about the activities of a committee hich is to study forms and results of antenatal training or the relief of pain in labour. To some of us who forears supported and advocated the establishment of a tate medical service, it has been a cruel disillusionment o find that, despite the great opportunities arising from he introduction of the National Health Service, so many ospitals have been content to provide some kind of "face-saving" ritual. Far too often this consists in iving the patient the face-piece of a gas-air machine, ithout due and proper regard being paid to the technique f pain-relief.

In the analgesia debate in the House of Commons, Mr. Peter Thorneycroft read some distressing letters from nothers, telling of their experiences. Yet this debate ailed to awaken the public conscience. Has even one egional hospital board created a research fellowship in nalgesia? In all the length and breadth of our land, nly one public authority, the Hertfordshire County Council, has gone to the trouble and expense of undertaking an investigation of new methods of analgesia, which could be of inestimable benefit to our mothers.

New Barnet. JOHN E. ELAM.

UTERINE DYSFUNCTION

SIR,—In your leading article of May 17 you present a vivid account of defective uterine action, and rightly stress that the condition is incompletely understood. It was disappointing to find no mention of the contributions made by S. R. M. Reynolds, who more than anyone has shed light on this dark problem. He has given us a clear account of normal uterine behaviour, and his is the concept of a gradient of activity from contracting fundus to passive mid-uterus and cervix. He has shown that this pattern of uterine activity may be disturbed, even reversed—a condition which causes delay in cervical dilatation. Likewise reminding us that the uterus is developmentally a paired organ, he has emphasised that incoördination of the action of its component halves can cause ineffective labour.

You quote Professor Nixon's experiments on the uterus in "mid-pregnancy" and his investigation of the effect of posterior-pituitary extract on the muscle-fibres of upper segment, lower segment, and cervix, and the differences he observed in response from the three regions; but it is well known, and was shown by Prof. Chassar Moir as early as 1934, that the response of the uterus to this extract is different in labour from its response in early pregnancy.

The evidence suggests that it is premature to insist, as you have done, that oxytocin always makes incoordinate uterine action worse. The analysis of recorded labours is more valuable than conjecture on this point, and experiments so far carried out in this department have shown clearly that in carefully selected cases dilute intravenous pitocin can promote normal labour even after days of incoördinate action. At the forthcoming congress at Leeds, it is proposed to present evidence in support of this contention.

Area Department of
Obstetrics and Gynæcology,
Oxford.
E. ARTHUR WILLIAMS.

MACROCYTIC ANÆMIA

SIR,—Describing the macrocytosis that develops during the treatment of certain cases of hypochromic anæmia in Uganda, Dr. Trowell[1] says that "this mysterious and rapid rise of the mean corpuscular volume (M.C.V.) under iron therapy does not occur when microcytic hypochromic anæmia is treated in Britain." If Dr. Trowell intends this to apply to cases of ankylostomiasis, I cannot have anything to say. Otherwise I would like to mention that at least six cases have been reported by Dr. Hawkins and his colleagues.[2] I agree that the superimposition of severe iron deficiency on a pre-existing macrocytic anæmia may depress the marrow with resulting hypochromic anæmia, which may become microcytic if the iron lack is great enough, whether or not there is any intestinal hæmorrhage.

In this part of the world at least, the microcytic variety of hypochromic anæmia is not so rare. I would group all hypochromic anæmias under three heads:

1. Those with a normal M.C.V., normal gastro-acidity curve, and a normoblastic marrow of the true iron-deficiency type. This variety is readily amenable to treatment with oral iron, and macrocytosis during treatment is confined to the period of reticulocyte response. Even then it is not very great.
2. Those with a normal M.C.V., moderate hypochlorhydria, and a hypocellular normoblastic marrow. This type does not respond to oral iron as promptly as the first group, while intravenous iron brings about a quick remission. Macrocytosis, if it develops, tends to persist a short time after the reticulocytosis has worn off.
3. Those with a low M.C.V., severe hypochlorhydria or achylia, and a distinctly hypocellular normoblastic marrow. In this type the normoblasts are much smaller than the classical cells, and the cytoplasmic fringe is so thin that they look more like free normoblast nuclei than intact cells. I have seen stray giant stab-cells in two such cases. There also appears to be, in many cases, some underlying disturbance such as endocrine defect, malignancy, or simply old age. Most of the patients in this group have defective fat absorption.

It is in the third group that I have noticed refractoriness to oral or parenteral iron. Therapeutic macrocytosis invariably develops, and once developed appears to be permanent, being uninfluenced by folic acid, liver extracts, or vitamin B_{12}.

Israëls and Sharp[3] have demonstrated megaloblasts in their cases of idiopathic steatorrhœa. I take it that the megaloblasts seen in cases of defective fat absorption are not far different from those seen in the sprue syndrome. When an iron defect is superimposed on this type of marrow, there is every possibility that it will undergo a normoblastic change. Incidentally, this conversion is effected through an intermediate dimorphic phase. If at the stage of established iron deficiency iron is administered, the marrow naturally reverts to its original megaloblastic character. The resultant macrocytosis is the phenomenon that we see as the macrocytic reaction in hypochromic anæmias under iron therapy. The giant stab-cells are probably the remnants left over from the original megaloblastic marrow of idiopathic steatorrhœa.

Dr. Hutton (Jan. 12) feels that the macrocytic "swing" in the treatment of hypochromic anæmia with iron is due to the replacement of the old microcytes by young macrocytes. In established iron deficiency the marrow does not show any megaloblasts—classical ones or precoctic cells—and it is therefore doubtful whether this could be the explanation. The term "precoctic" should be a welcome addition to hæmatological nomenclature. An appeal similar to that by Dr. Lehmann (Feb. 9), to recognise the cell representing intermediate erythropoiesis, was made by the late Dr. S. K. Sundaram.[4]

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[1] Trowell, H. C. *Lancet*, 1951, ii, 761.
[2] Hawkins, C. F., Peeney, A. L. P., Cooke, W. T. *Ibid*, 1950, ii, 387.
[3] Israëls, M. C. G., Sharp, J. *Ibid*, i, 752.
[4] *Ibid*, 1948, i, 568.

The only difference was that Dr. Sundaram described the cells as macronormoblasts brought into being by sustained and profound stress on the marrow. I have seen this type of cell in many cases of macrocytic anæmias where a chronic, untreated disorder is present.

Dr. Trowell's case of pernicious anæmia presents a few interesting points:

1. A single massive dose of liver extract, expected to act over 150 days, was given in a case of macrocytic normochromic anæmia with a megaloblastic marrow. The reticulocyte response was up to expectations; but even after the reticulocyte response disappeared the increase in M.C.V. persisted. The macrocytosis, as judged by the M.C.V., continued even with administration of folic acid and vitamin B_{12}. This stubbornness on the part of the M.C.V. in true megaloblastic anæmias under adequate treatment has never been noticed by me. Incidentally, was the use of folic acid (over 400 mg. in 5 weeks) considered safe in view of the diagnosis of pernicious anæmia?

2. There is no mention of the Wassermann reaction having been tested in this case. I attach some importance to this, because I have noticed that in macrocytic anæmia with a positive Wassermann reaction, though remission of the anæmia takes place with proper treatment, the macrocytosis persists until the syphilis is treated.

3. The initial hæmogram shows a relative lymphocytosis of over 70%. In my opinion, this would indicate a silent infection; and I feel that antibiotics or chemotherapy might have been indicated.

It is possible that the points I have raised do not apply to this case if the average normal African has an M.C.V. of over 100 c.μ. I would very much like to know whether in this case the marrow contained any of the precoctic cells of Dr. Lehmann.

Trichinopoly, South India. M. S. NARAYANAN.

EXPERIMENTAL PULMONARY HÆMOSIDEROSIS

SIR,—Your annotation of May 31, regarding the experimental production of pulmonary hæmosiderosis,[1] draws attention to the concept of bleeding into the lungs from the mucosa of the terminal bronchioles at the site of the anastomoses between the bronchial and pulmonary circulations.[2]

Normal anastomoses between arterioles of more than $60\ \mu$ at that site have so far not been demonstrated, and if anastomoses exist near terminal bronchi they must be at capillary level—i.e., at the end of the alveolar ducts; the existence of even these has not been verified histologically.[3]

Bronchopulmonary anastomoses have been demonstrated in a variety of conditions, including mitral stenosis. The methods employed usually showed these to be proximal to the capillary bed. Wood and Miller[4] observed anastomoses radiographically in mitral stenosis with right ventricular hypertrophy, using an injection mass too coarse to penetrate the capillary beds. As subsequent histological studies were not carried out, the site of these anastomoses must be inferred; it is unlikely to have been at the level of the capillary beds.

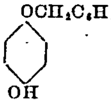
In my own limited experience, occlusive changes in some branches of the pulmonary arteries, following infarction, have led to proliferation of the vasa vasorum into the occluded lumens. These vessels are branches of the bronchial arteries, and are normally more than $100\ \mu$ in diameter. By recanalisation of the pulmonary arteries, permanent bronchopulmonary anastomoses are established; and the site of these anastomoses, in my experience, is usually near medium-sized pulmonary arteries and proximal to the smaller bronchi. Other types of precapillary anastomoses have not been observed. It might, therefore, be reasonable to assume that similar changes had occurred in the lungs studied by Wood and Miller.

Bronchopulmonary precapillary anastomoses, though not uncommon, are usually of pathological significance; and the site of their production is anatomically not related to the terminal bronchioles as Lendrum et al. assumed.

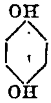
St. Stephen's Hospital,
London, S.W.3. LEON CUDKOWICZ.

DEPIGMENTATION OF SKIN BY QUINOL AND ITS MONOBENZYL ETHER

SIR,—Quite recently I came across a case of depigmentation which is of interest in view of observations by Oliver et al.[1], who described depigmentation by the monobenzyl ether of quinol (I).



I



II

The circumstances were as follows:

In a Chicago tannery where the operatives wore rubber gloves to protect their hands, the skin of Negro and Mexican workers was observed to become decolorised over the backs of the hands and up the forearms, corresponding to the area covered by the gauntlet gloves, and the cause was found to be the anti-oxidant (I) embodied in the rubber to prevent ageing. This compound was thought to be dissolved out of the rubber either by the alkalis which the operatives were handling, or by perspiration, or by a combination of both, and hence would be in an absorbable state when coming into contact with the skin. Its effect was to prevent the formation of melanin by inhibiting one or more of the series of oxidation reactions whereby the pigment is produced in vivo from an adrenaline-like precursor.[2 3]

My own observation was of depigmentation in the fingers of a Negro who was continually handling photographic chemicals, including quinol (II) as developer. It would appear, therefore, that quinol has the same effect upon skin pigmentation as the monobenzyl ether (I), in that it acts as an anti-oxidant. This is of interest in view of the fact that the American workers suggest that the unsubstituted quinol plays no part in the phenomenon.

London, S.W.10. JOYCE A. DUFFIELD.

KWASHIORKOR

SIR,—The ætiology of kwashiorkor is still by no means settled. In connection with the paper by Dr. Thompson and Dr. Trowell (May 24), I should like to record the following observation, which will be described more fully elsewhere.

Cases clinically indistinguishable from those reported from Uganda occur widely in India. In four of our cases in India histological evidence showed that the defect might be a congenital vascular or cardiovascular abnormality. In these cases vascular malformations were seen in almost all the organs of the body; and particularly the liver, spleen, kidneys, pancreas, and even sections of tongue and skin showed vascular malformations. The endocardium was thickened in all these cases, and thickening of the mitral cusps had produced signs of congenital heart-disease in life.

It seems that this generalised vascular defect is congenital; and, being so widespread, it is perhaps a factor of primary importance. It seems likely that at least some cases of kwashiorkor may be due to this congenital abnormality. I am not aware whether Dr. Trowell and his colleagues have noticed this in any of their cases.

I am not suggesting that this is one of the main or even one of the important causes of the disease; but only

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[1] Magarey, F. R. *J. Path. Bact.* 1951, 63, 729.
[2] Lendrum, A. C., Scott, L. D. W., Park, S. D. S. *Quart. J. Med.* 1950, 19, 249.
[3] Miller, W. S. The Lung. Springfield, Ill., 1947.
[4] Wood, D. A., Miller, M. *J. thorac. Surg.* 1938, 7, 649.

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[1] Oliver, E. A., Schwartz, L., Warren, L. H. *Arch. Derm. Syph.* 1940, 42, 993.
[2] Raper, H. S. *Biochem. J.* 1927, 21, 89.
[3] Burton, H. *Chem. Ind.* 1948, p. 313.

that it is one which it has been possible to demonstrate post mortem in four of our cases. How important it is, only time and further study will show.

London, W.2. S. L. MALHOTRA.

EPILEPSY AFTER AN INJECTION

SIR,—Reactions of the type mentioned by Dr. Bell (May 24) may occur after any slight trauma such as an injection, and it is therefore improbable that the giving of penicillin was the cause of the symptoms he mentions. I have seen such symptoms follow immediately on vaccination, on the taking of a blood sample (although done with ease by an experienced operator), and on injection of tryparsamide. In each of these cases the patient was a healthy man. It is interesting that Dr. Bell's patient was a woman, as in an experience of many thousands of injections to both sexes I have never seen an epileptiform attack ensue in a woman.

The condition is alarming at the time, and in my experience there is a phase of postictal confusion for up to an hour. So far as I know, the patient may have no other epileptic attack; but it is reasonable to suspect that the needle-prick acts as a trigger stimulus, just as a flickering light can induce an epileptic attack in quite a number of people who are not ordinarily subject to epilepsy. It would be most interesting to know if there is any information as to electro-encephalographic findings in any patient who has thus reacted. The condition does not seem to be identical with the dramatic reaction which rarely follows an intravenous injection of neoarsphenamine.

Strangely enough I have never seen a convulsive reaction follow the more alarming (to the patient) procedure of lumbar puncture; nor have I seen it produced by clumsy technique.

Accrington. R. C. WEBSTER.

PROLONGED USE OF NIKETHAMIDE

SIR,—For years now, nikethamide has been used as an analeptic and stimulant which combines great efficacy with a wide margin of safety. Reports on it number well over 2000; yet one aspect of the properties of this substance still seems to be insufficiently appreciated. This is that, owing to its rapid excretion from the body, it may be given for months and even years on end without fear of tolerance or untoward side-effects.

As early as 1931, Marck[1] reported that patients who had taken nikethamide for considerable periods noticed "a sensible improvement in their respiration and general condition." In 1939, Verlende[2] described consistently good results with prolonged treatment; and two years later, Arany[3] observed that "the administration of Coramine for months, or even years, never leads to weakening of its effect; tolerance does not develop."

Clinical observations show beyond all possible doubt that, in treating respiratory and circulatory disorders, nikethamide may be given continuously for very long periods without danger. Given by mouth, it is excreted within 3–6 hours, according to the dose. Thus it has no cumulative effect. This explains why the same dosage gives an equal effect, even after years of administration.

The following are three illustrative case-records.

CASE 1.—A widow, aged 85, was seen on the night of March 28, 1946, during an attack of cardiac asthma. She had severe dyspnœa; her pulse-rate was 120 per min. and blood-pressure 160/100 mm. Hg. She had had hypertension with blood-pressure varying from 200/120 to 180/100 for more than fifteen years. She was given 'Pantopon' gr. $^{1}/_{6}$ with atropine gr. $^{1}/_{120}$, ouabain 0·25 mg. intravenously, and nikethamide 5 ml. intramuscularly. The attack abated in three hours but milder attacks took place on the following two nights. Nikethamide 15 minims was given thrice daily after meals for a week, and then twice daily. The patient's vision failed within the next few months and she remained indoors for most of the time; this helped in the recuperation from the heart disorder, but mild attacks of dyspnœa persisted. She continued taking nikethamide 15–20 minims once or twice daily for the next five years. In March, 1950, she had influenza, with a temperature of 102°F for three days. Penicillin was given and the temperature dropped to normal; but the patient had repeated attacks of cardiac asthma, and ten days later she died.

CASE 2.—A married woman, aged 65, was seen on March 3, 1951, with severe retrosternal pain, which had started suddenly during the night. Her pulse-rate was 132 per min., temperature 97·6°F. She was found to have coronary thrombosis and was treated with heparin, nicotinic acid, papaverine, and rest in bed. From the start she received nikethamide 15 minims thrice daily, and later twice daily. With this her dyspnœa improved. She now takes nikethamide 5–20 *minims whenever she feels dyspnœic or faint.*

CASE 3.—A married man, aged 51, was seen on Sept. 28, 1946, with severe retrosternal pain which had begun during the night. Electrocardiography showed coronary occlusion. He was put on heparin 5000 units six-hourly with nicotinic acid 50 mg. thrice daily. The laboured respiration did not improve, however, until nikethamide 20 minims thrice daily was administered. This dosage was continued for a week, and the drug was then given once or twice daily for five weeks. The patient is now taking it whenever his respiration becomes laboured, with great relief. For about five years now, he has owed his life to nikethamide.

Cairo. I. K. GAYID.

CALCIFEROL IN PULMONARY TUBERCULOSIS

SIR,—Last year Fielding and Maloney[1] described the use of massive dosage of calciferol with streptomycin and *p*-aminosalicylic acid (P.A.S.) in the treatment of pulmonary tuberculosis. They suggested that, in their cases with gross cavitation and high temperature where no good response to streptomycin and P.A.S. alone could be expected, simultaneous calciferol ('Sterogyl 15') injections potentiated the effect of the chemotherapy and an unexpectedly good result was obtained. This was attributed partly to increased penetration of streptomycin into the cavity walls and partly to a sclerosing effect at a rather later stage. Both hypotheses were based on the observed effect of calciferol on the lesions of lupus vulgaris. Unfortunately, the number of cases was very small, and there was no control series.

A controlled trial of calciferol given with streptomycin and P.A.S. has been made at Clare Hall Hospital. In view of the fact that at least two drug firms have advertised preparations of calciferol for use with streptomycin in pulmonary tuberculosis it seems important that these results should be recorded.

In this trial two unselected groups were obtained by alternate cases in one male and one female ward starting course of streptomycin and P.A.S., receiving in addition weekly injections of sterogyl (600,000 units). From laboratory sensitivity tests or for other reasons it could be assumed that all of the 42 cases involved in the trial had bacilli which were still sensitive to streptomycin.

Results were assessed on the radiological change after six weeks' treatment, by an observer with no knowledge of the treatment group of the patients. Cases were classified into three groups: (1) little or no improvement, (2) moderate improvement, and (3) marked improvement. No case in the control or test group deteriorated whilst under treatment, although 1 in each group did so some weeks after treatment had ceased. It appeared that the calciferol cases did no better than the others, and in fact the total scores in each group were almost equal. When the cases with gross cavitation, forming about one-third of the whole series, were considered separately, there was again no beneficial effect attributable to calciferol. In a few of the sterogyl group the chemotherapy was continued for a further six weeks without any noticeable radiological change.

Two points emerge from this investigation: (1) calciferol does not notably enhance the action of streptomycin and P.A.S. in any of the common forms of tuberculous pulmonary disease; and (2) where calciferol is covered by streptomycin and P.A.S., *active pulmonary tuberculosis is not a contra-indication to its use.*

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[1] Marck, A. *Fortschr. Ther.* 1931, 7, 124.
[2] Verlende, J. *Scalpel, Liége*, 1939, 92, 125.
[3] Arany, G. *Ars Medici*, 1941, 31, 502.

[1] Fielding, J., Maloney, J. J. *Lancet*, 1951, ii, 614.

Clare Hall Hospital,
South Mimms, Barnet.
STANLEY L. O. JACKSON.

NERVOUS CONTROL OF SWEATING

SIR,—In your interesting annotation of April 26 no mention was made of a method of controlling essential hyperidrosis of the palms which I feel deserves to be more widely known. It consists in the paravertebral injection of 5 ml. of 6% aqueous phenol in the vicinity of the 2nd thoracic sympathetic ganglion and a similar amount in the region of the 3rd thoracic ganglion. This procedure should of course be preceded by a diagnostic block using 1% procaine in the same amounts.

The results appear to be dramatic and lasting, a Horner's syndrome *is avoided, and in my experience* subsequent intercostal neuritis has not occurred.

Hull.
W. N. ROLLASON.

CONTROLLED HYPOTENSION AND ITS EFFECT ON RENAL FUNCTION

SIR,—It seems to me that Dr. Evans and Dr. Enderby (May 24) have misinterpreted their results. Accepting that twice the standard error of the difference could be statistically significant, "proteinuria persisting for more than three days" after hexamethonium administration should be accepted as a significant figure. However, I would particularly like to emphasise that their results *do not* show that renal function is not appreciably impaired, but simply that their data are an insufficient basis for a positive statistical conclusion. The differences they observed *could* be due to chance, but they also *could* be due to hexamethonium administration; and in fact proteinuria persisting for more than three days, *on their own figures, is probably not due to chance.* They would, I feel, have been better justified in concluding *that their figures are suggestive of renal damage* though not statistically conclusive. I cannot see how *they can arrive at a reverse conclusion.*

Oldchurch Hospital,
Romford, Essex.
S. LOCKET.

WHAT SHOULD THE NURSE BE TAUGHT?

SIR,—I was very glad to see that some of your correspondents have condemned the practice of employing girls of 15 as pre-student nurses. To the objections they have raised I would like to add two more. Firstly, I feel that nursing puts a great emotional strain on the young adolescent with which she is not yet equipped to deal. As far as the patients are concerned she is a nurse in uniform and they treat her as such. She sees and hears things which, with her limited experience of life, she cannot fully comprehend, and consequently she often gets a warped and wrong view of the situation. My second point is that the nurse who started her career at 15 emerges at 21 a fully trained nurse with a great deal of knowledge about the sick but very little knowledge or experience of life outside the hospital walls. Her life was ordered and directed for her at school, it is further directed and ordered for her at the hospital. How much better would it have been if before entering the hospital the nurse-to-be had taken a job or even stayed at home and helped mother to deal with the butcher and baker and grocer. The patient expects the nurse to be an experienced adult, not a specially instructed school-child.

The nurse in training at the present time is in a most peculiar position. She is courted and bullied in turn and does not know where she stands. Her duties in one working day may vary from that of a cleaner to that of a staff-nurse or even a sister. It does not give her either contentment or sense of achievement or a sense of security. She is just as bewildered in the classroom. Her curriculum is a hotchpotch of old, outdated applications, modern chemotherapy, much too detailed anatomy and physiology, and only the merest suggestion of psychology. The curriculum is trying its best to keep up with the increasing responsibilities of the nurse in the ward, with the modern advances in medicine, and at the same time is still teaching how to apply blistering lotions, cupping, and the like. The position of the nurse in the hospital, and her training (practical and theoretical), must be revised, clarified, and standardised. It can only be done by a joint effort. The time is long overdue for the medical and nursing professions to confer and evolve a system of "basic nursing" shorn of the impedimenta of obsolete and discredited procedures, with at least a standard anatomical terminology common to doctor and nurse, and cleansed of the vast accretion of irrelevant knowledge which now encumbers the curriculum.

SISTER TUTOR.

Medicine and the Law

Hospital Board versus Professional Staff

WE had not long to wait for a striking example of the *situation to which Prof. Ian Aird lately drew attention,*[1] where some allegation of want of care creates discord between hospital managers and their professional *staff over their relative responsibilities* in the law-courts.

Last July, Mr. Justice Oliver awarded Mrs. Gladys Jones £1438 3*s.* 3*d.* damages in respect of the death of her husband in the following circumstances as stated in the Court of Appeal.[2] In January, 1951, Mr. Jones was admitted to a Manchester hospital, suffering from facial burns. A doctor who had qualified in 1949 was on duty as anæsthetist in the casualty department. She and a senior colleague decided to dress the burns under an anæsthetic. They first used gas and oxygen; but the mask impeded the dressing. A supply of thiopentone was therefore sent for, and the first doctor, who was a defendant in the case, injected 10 ml. intravenously in two shots at an interval of some seconds. The patient being already partly anæsthetised, the usual test of his response by making him count out loud was not practicable. The patient died almost immediately. His widow sued the defendant doctor on the ground of negligence and the Manchester Regional Hospital Board on the ground of its vicarious responsibility as her employer. Mr. Justice Oliver gave judgment against the doctor and the board. He next had to try cross-claims brought against each other by these two defendants each claiming an indemnity or a contribution from the other under section 6 of a Law Reform Act of 1935. The board's case was that the doctor was liable, because it was an implied term of her contract of employment that she warranted herself to possess reasonable skill and undertook to exercise it in her employer's service. The judge held the board 100% responsible. *It had,* he thought, "asked for trouble" in putting a weapon like thiopentone within reach of a recently qualified doctor and expecting her to handle it with the necessary skill and experience. Against that decision the board appealed with, as will be seen, limited success.

In the Court of Appeal Lord Justice Singleton *thought* it might be said that the board was entitled to expect the defendant doctor to have the knowledge and skill of someone newly qualified; but there must also be implied an undertaking by the board to provide some reasonably competent person to work with, or guide, her in case of difficulty. There was *in fact another doctor,* not a party to the litigation, working with her at the time. It was this other doctor who decided to start with the mask and nitrous oxide—" a wholly unintelligible and futile proceeding which was perhaps the originating cause of the trouble." The other doctor was the senior; he also was a servant of the board; there seemed no difference between his responsibility and that of the defendant doctor. On the facts of the case the board's claim to an indemnity from the defendant doctor must fail, but it was impossible to hold that she had no share in the responsibility for damage or that her share was merely nominal. Lord Justice Singleton said he would allow the appeal to the extent of apportioning the liability at 80% on the part of the board and 20% on that of the doctor. Lord Justice Denning concurred. He doubted if there was any common-law principle that, if a master is sued for the negligence of a servant, their contractual relationship impliedly entitles the master to an indemnity from the servant. A servant promises to do his best, but a promise to indemnify his master against liability to third parties ought not to be implied. The board's claim was not at common law but under the 1935 Act. The Act made it a matter for the discretion of the court whether any, and if so what, contribution or indemnity should be ordered. The Lord Justice went on to remark that it would be in the highest degree unjust if hospital authorities, by getting inexperienced doctors to perform their duties for them without adequate supervision, could throw all the responsibility on to those doctors as if they were experienced practitioners. Both doctors here had been responsible, but the responsibilities of the hospital authorities were greater than those of either doctor. " They should so run their hospital that mistakes of this kind did not occur."

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[1] *Times,* May 23, 1952; see *Lancet,* May 31, 1952, p. 1117.
[2] *Times,* May 30, 1952.

The third member of the court, Lord Justice Hodson, dissented. The defendant doctor, he said, had a duty to administer anæsthetics in the casualty department when required. It had not been established that she was not to be trusted to employ a regularly used anæsthetic without supervision by someone more experienced. Disagreeing with Lord Justice Denning, he considered that the common law did infer a warranty by the employee in this case; her failure to exercise reasonable skill and care was a direct cause of the damages. He himself was prepared to allow the board's appeal and to order a contribution of 100% by the defendant doctor. The majority decision of the court, however, limited the contribution to 20%. Leave was granted for an appeal to the House of Lords. Further comment must therefore be suspended until the final appellate tribunal has said the last word.

Cruelty Charge Fails

The trial at Dorset assizes of the Rev. P. E. Wallbridge and his wife, joint principals of Farney Close School at Lytchett Minster, on charges of ill-treating a 14-year-old boy, is a reminder that there are usually two sides to a case. In December, 1951, the school pupils—mainly mentally maladjusted children, some virtually imbeciles, and others largely of reasonable intelligence—ranged in age from 5 to 17 and numbered about a hundred. The chief witness for the prosecution, Mr. Gell, the Dorset county children's officer, described how he found the boy in a long narrow room in an outhouse, where the only furniture was a tin can and an iron bedstead with a wire mattress. On the bedstead there were some filthy blankets, no pillow, and no mattress. The boy, who was asleep, was naked. He had no nightclothes; his ordinary dayclothes were on the stone-flagged floor. It was a cold night. There was a door at each end of the room; one was bolted, the other padlocked: he could not have got out; there was no apparent means for him to get into touch with anyone outside, if he wanted to.

The father of the boy gave evidence that his son was difficult, a bed-wetter, destructive, and untrustworthy. Put to bed in pyjamas, he would be found naked in the morning. He would tear up his sheets, blankets, and pillowcases. His parents locked the boy up at night: he seemed to take that as a matter of course and was quite placid about it. His letters from school seemed to show that he was happy, but Mrs. Wallbridge wrote that he could not remain after Christmas as his general behaviour had deteriorated. The father said he did not think the outhouse unsuitable during a punishment period. Mrs. Wallbridge gave evidence that the boy's habits were dirty. He was moved from a dormitory because it was unfair to his companions to keep him there. He was put into a room by himself, but he made it uninhabitable. He was placed in the outhouse because it had a stone floor and the doors at each end provided a drying draught after the floor had been scrubbed. It had once been a sitting-room. Until he was locked in, he prowled about the buildings at night, turning on taps and lying for hours in a hot bath in the middle of the night. There were two State-registered nurses on her staff; every possible method had been tried to cure the boy of bed-wetting. Mr. Wallbridge testified that for three weeks he had got up every hour of the night to try to cure this. His wife was utterly devoted to the children. The matron, a State-registered nurse, gave evidence that she considered the sleeping conditions right for that particular boy. The medical officer of the school said the general health of the children was good; he could not believe the boy was suffering from cold if he was asleep.

At the close of the case for the prosecution the judge said he was prepared to hold that there was no evidence on which the jury could convict the male defendant, who took no part in the household management. At the close of the defence the jury acquitted Mrs. Wallbridge.

It was a typical case for a jury, after seeing the witnesses and hearing the evidence, to decide. The propriety of the verdict is not to be questioned, even if the conscience of the community is at present made uneasy by a series of distressing allegations of cruelty towards children up and down the country.

Fatal Laryngeal Spasm

An inquiry was held at Stranraer on May 21 into the death of an 11-year-old girl after an anæsthetic. She had injured her leg on May 17, and an orthopædic surgeon, to whom she was later referred, advised that the leg be manipulated and put in plaster.

The surgeon said in evidence that he had been expecting the girl's doctor to come to the hospital on the afternoon of the operation, but when he did not arrive he decided to act as anæsthetist himself. The operation was performed by one of the hospital sisters. The patient was healthy and indulged in strenuous exercise, and he had not thought a medical examination necessary. When he began giving ether she quickly stopped breathing, and he was not sure how much she inhaled. He took the mask from her face, turned her head over, and pulled out her tongue with forceps. After trying artificial respiration without success, he ordered the sister to give the girl a stimulant. As there was still no response, he replaced the mask and pulled what he thought to be the oxygen by-pass lever on the anæsthetic machine, but after a time he found that he had pulled the wrong lever and that nitrous oxide was being delivered. He felt sure, however, that the girl did not inhale any of it. As soon as he realised his mistake, he changed to oxygen. He again tried artificial respiration; the girl then took a breath and recovered to some extent. He suggested that the girl be kept in hospital overnight, and he then handed over the case to another doctor. The child died during the night.

The surgeon said that considerable cerebral damage must have taken place before breathing was restored. He attributed the condition to laryngeal spasm caused by the ether. The sheriff reminded the jury that the spasm developed before the mistaken administration of nitrous oxide. The evidence did not seem to indicate that the mistake had anything to do with her death. He pointed out that while the patient might have been medically examined before the operation, it did not seem to be necessary when the operation was slight and the patient was a healthy child. The jury returned a verdict of death from anoxæmia of the brain and medulla after the administration of an anæsthetic.

Public Health

Inoculation Against Diphtheria

A Ministry of Health circular to local authorities (15/52), discussing inoculation against diphtheria, says:

> "It is vital to secure that not less than 75% of babies are immunised before their first birthday. A recent special investigation has shown that the highest rate of immunisation in the first year of life so far achieved has been only about 55%—the 75% proportion being attained only for children aged 2 or over at the time of the interview (May, 1951). It is estimated that the number of children under one year old immunised during 1951 was 185,000. This is only 28% of the estimated number of children reaching the age of one year during 1951."

Diphtheria deaths and corrected notifications for England and Wales since 1944 have been as follows:

Year	Deaths	Corrected notifications
1944	934	23,199
1945	722	18,596
1946	472	11,986
1947	244	5609
1948	156	3575
1949	84	1890
1950	49	962
1951	34*	699*

* Provisional.

The circular calls for sustained publicity to inform parents that diphtheria is still a serious threat. One of the posters now being issued by the Ministry reads: "If you had *seen* a baby with diphtheria you would have yours immunised now."

Births, Marriages, and Deaths

BIRTHS

Barker.—On May 26, at Much Hadham, Herts, to Barbara (née Summers), wife of Dr. David Barker—a daughter.

Jones.—On May 26, at Cardiff Royal Infirmary, to Pauline (née Jackson), wife of Mr. Hugh Owen Jones, M.S., F.R.C.S.—a son.

Nixon.—On May 24, at Gally Hill Nursing Home, to Pamela (née Magee), wife of Dr. Peter Nixon—a daughter.

Pencheon.—On May 25, at Leeds Maternity Hospital, to Pamela (née Ashworth), wife of Dr. J. M. Penche

Powell.—On May 28, at the Royal Infirmar
Jean (née Courts), wife of Dr. Glyn D.

MARRIAGES

Brown—Saxon.—On May 24, at Chester, Austin Brown, F.R.C.S., to Catherine Rosemary Saxon.

DEATHS

Beggs.—On May 28, Herbert Tennison Beggs, L.R.C.P.I., of The Old Vicarage, North Petherton, Bridgwater, aged 61.

Cox.—On May 24, Richard Percy Cox, M.D. Edin., late of Ealing and Manchester, aged 94.

Mackenzie.—On May 20, in Aberdeen, Mary Meta Mackenzie, M.B. Aberd., D.P.H.

Paterson.—On May 19, at Eltham, James Lee Hamilton Paterson, M.B. Edin., aged 68: formerly medical superintendent of the Lester Chinese Hospital, Shanghai.

Pennefather.—On May 28, at Harrow-on-the-Hill, Claud Maxwell Pennefather, M.D. Durh., aged 75.

Stock.—On May 30, at Dorrington, Porthill, Stoke-on-Trent, William Stuart Vernon Stock, M.B. Lond., F.R.C.S., formerly of Clifton, Bristol, aged 79.

Walmsley.—On May 28, at Dorking, Stephen Elliott Walmsley, M.R.C.S., late of Birmingham.

Warner.—On May 24, Allan Warner, M.D. Durh., D.P.H., of Desford, near Leicester, aged 81.

Woodhouse.—On May 29, at Blandford St. Mary, Dorset, Francis Decimus Woodhouse, M.R.C.S., D.P.H., aged 88.

Notes and News

INTERNATIONAL PHARMACEUTICAL STANDARDS

The World Health Organisation's expert committee on th *International Pharmacopœia* has made its ninth report.[1] Th preparation of vol. 2 is proceeding; the demand for vol. 1 published on Oct. 30, 1951, has necessitated a second printin of the English edition. The subcommittee which has bee considering the subject of non-proprietary names suggest that a manufacturer who wants a name for a new drug shoul notify W.H.O. through his national pharmacopœia commissio or national health administration. The report recommend that new names be selected at an international level if possibl An appendix gives a list of the Latin, English, and Frenc non-proprietary names for various drugs together with th appropriate chemical names agreed upon by the subcommittee

FOOT-AND-MOUTH DISEASE

In our annotation of May 24 we emphasised that the viru of foot-and-mouth disease is always imported into thi country from abroad, and that endogenous spread can bes be controlled by slaughtering infected animals and thei contacts. The Ministry of Agriculture now reports tha young calves, with few if any signs of the disease, may spread the virus to healthy stock. A batch of calves from th south apparently became infected on the way to northern markets, and it was the scattering of these animals which led to the national standstill order. Some of the calves died. Others showed no visible lesions, but laboratory tests proved that they were infected and presumably infective. Important and disturbing as this new observation is, it does not, at present, affect the validity of the present policy o control; for these atypical infections may have been with us for some time. It may be difficult to convince farmers that the slaughter of some 45,000 farm animals has been necessary, but the demonstration of atypical infection in calves further justifies this course.

UNIVERSITY OF OXFORD

The clinical school of the university has been growing steadily, and it now takes 32 students a year, mainly from the Oxford preclinical course but also from other universities in Britain and the Commonwealth. Accordingly, the administrative machinery of the school has lately been revised. The board of the faculty of medicine, which represents preclinical and clinical interests, is still to direct the general policy of the school, but responsibility for clinical teaching and finance in the clinical school is to be delegated to the Nuffield Committee for the Advancement of Medicine. To fulfil its new duties the constitution of the committee has been widened, and the board of governors of the United Oxford Hospital and the Oxford Regional Hospital Board will now be represented on it. It will, however, appropriately retain the name of Nuffield Committee, for 6 of the 17 members include that name in their designation.

A WELL-CONTROLLED BIRTH

When a mimeographed sheet of domestic news turns into a printed quarterly we may say that the pregnancy is safely over, and the child out in the world. *Family Planning*, the new bulletin of the Family Planning Association,[2] wears in its first issue something of the fœtal look proper to the newborn. Its anxious parents and nurses perhaps need reminding that every little journal must have advertisements as well as copy if it is to thrive. These will be forthcoming no doubt, and meanwhile the dimensions of the thin little newcomer must not be taken as indicating a poor capacity for growth. We hope to see it more than double its birth weight in the first three months.

University of Cambridge

On May 24 the degree of M.CHIR. was conferred on Thomas Fenwick.

The Health and Welfare of the Family

Prof. Leslie Banks is to speak at a conference on this subject which the public-health section of the Royal College of Nursing is holding in the Cowdray Hall, Henrietta Place, London, W.1, at 2.15 P.M. on Saturday, July 5.

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[1] *World Hlth Org. techn. Rep. Ser.* no. 50, 1952. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1. Pp. 33. 2*s.*

[2] 64, Sloane Street, London, S.W.1.

niversity of London

The following have passed the final examination for the egree of M.B., B.S.:

Honours.—R. L. B. Beare, Oliver Dansie, H. T. Davies, J. A. leming, Grace E. S. Forrest, E. D. Fox, E. J. G. Glencross, braham Guz, R. F. Jackson, Da[illegible]ett, O. P. Newell, P. M. Phillips, [illegible]al, illian E. M. Tarnoky, D. W. Ver[illegible]

Pass.—Pauline A. Adams, R. K. Allday, G. A. Ames, A. G. Amias, A. Andrews, J. R. Andrews, T. C. R. Archer, B. K. Arthur, R. Aston, K. D. Bagshawe, R. C. Baillie, Elizabeth M. R. Bakirjian, G. T. Balean, G. V. Balmforth, P. J. Barclay, S. S. Barker, T. C. Barlow, Mildred M. E. Barnard, Rosalind A. Barnes, W. B. Barnett, P. K. M. Barrett, W. G. Barry, F. J. Bateman, N. Bates, D. H. Bayton, H. S. Bedson, C. L. Belcourt, J. S. eresford, Hilary A. Berry, Phyllis E. Billinge, E. W. G. Birch, W. Bisset, A. S. Blake, W. R. Blatchley, J. N. Blau, D. G. luett, H. M. J. Bogaerts, R. F. Bolam, J. P. Bomford, Gisela Boss, O. W. Boyd, E. A. Boyse, D. W. Bray, L. H. Brearley, John rittain, R. W. Brotherwood, F. P. Brown, G. L. Brown, Helen E. rown, J. D. Bruce, C. J. Buckingham, I. H. Buckland, C. V. ullen, H. A. Burgess, Winifred Burgess, A. M. Burnford, T. K. H. urnham, J. D. K. Burton, Alison M. Bush, D. G. Calvert, H. J. Carne, M. Carter, Stephanie J. Carter, J. D. H. Cave, Jack Cherry, E. Clapham, Sylvia J. Clapp, J. A. Clappen, Barbara C. Clark, L. Clarke, R. J. S. Clarke, Heather R. Clay, R. C. Cochrane, aurice Cohen, F. J. J. Coleman, C. M. Conway, Josephine Cook, S. Cookson, P. B. Counsell, Barbara M. St. J. Coventry, Mary rawford, Etain A. Cronin, Lawrence Crouch, D. L. Crowther, aphne I. L. Da Costa, T. A. Daff, Melfyn Davies, M. L. Davis, H. Day, J. R. Deacon, L. C. Dean, A. J. H. de Kretser, John ennis, M. F. Dixon, J. S. Dodge, Josephine Dolan, W. A. C. ow, Marie G. Drew, H. T. Duke, John Eastwood, P. S. Elias, S. K. Essame, A. J. Evans, R. R. Evans, N. H. Eve, E. J. Fairlie, P. Farrell, I. R. Ferdinand, Elizabeth Fincham, Paul Fincham, F. Fisher, Boris Fistein, W. P. Fitt, Freda Fleischer, D. J. Flight, J. Flight, H. T. Ford, A. D. Fox, R. E. Frears, Paul Freilich, va A. Frommer, N. P. H. Gibbs, C. H. Gill, J. A. Girling, L. P. oodchild, A. H. Goodspeed, J. A. Gorst, Hilary B. Gostling, L. Granville-Grossman, Elizabeth I. Greenlaw, D. F. Hadman, G. Hamilton, D. O. Hancock, R. L. Hardway, D. C. Harris, ames Harrop, John Hart, J. D. Harte, Charlotte Hartstein, B. Hawes, E. G. Haydon, J. H. Heard, F. L. P. Heber, John Heckford, P. A. Henderson, Josephine C. M. Heylen, B. K. Higgins, [illegible] ighman, N. A. Hiley, J. M. Hill, R. F. [illegible] ony, W. D. Hopkins, D. J. Hosking, [illegible] Hughes, F. C. Hurrell, Bernard Hynes, [illegible] Isaac, B. G. Jackson, D. A. T. Jackson, Allan Jacobs, E. R. ohns, Isabel D. Johnson, A. O. Jones, Marie H. Kallberg, P. E. apff, Joan Kelly, P. J. King, Sylvia L. Kingsbury, R. M. Kirk, T. Knudsen, D. B. Laird, B. D. Lascelles, Barbara Lawrence, hyllis G. Lemon, Emanuel Lewis, C. A. Linsell, H. I. Lockett, D. Lord, K. R. Lown, Margaret Luing, D. J. McBrien, N. B. cDiarmid, D. A. F. McGill, S. N. Maclennan, Iain Macmillan, amela M. McMorran, David McQueen, D. J. Manton, G. A. Marin, W. Markham, I. G. Marsh, C. R. A. Martin, W. A. Matheson, oan M. Mawer, D. C. Mayr, P. D. Meers, Geeta Shrimukh Mehta, Morag J. R. Millar, H. A. Milne, C. A. C. Mims, D. N. Mitchell, [illegible] edhar, J. D. Moore, C. W. Morley, [illegible] orrison, K. E. Mortimer, D. A. J. [illegible] I. Newton, R. G. Newton, R. G. [illegible] Jean J. S. Nicolson, Margaret A. orman, Joyce B. Nunneley, R. M. Oliver, C. H. Opie, J. A. Page, S. Painter, C. A. L. Palmer, R. A. Pargiter, J. C. Parkes, P. M. Pawsey, Mary C. Peard, Millicent J. Pentney, K. C. Perry, L. J. Phillips, H. B. Polak, N. T. Pollitt, K. R. S. Pool, G. H. G. Poole, M. E. A. Powell Felicity Prestige, G. C. Pretty, E. C. V. Price, H. Price, M. G. Price, Freda E. Prince-White, F. N. Prior, D. A. [illegible] M. Ranken, Valery Rayner, R. A. S. Redd, V. J. [illegible] Rees, H. S. Reeve, G. H. Renton, J. M. Ritchie [illegible], R. B. Robinson, J. A. Rogers, Eleanor T. Rolston, [illegible] H. B. Ross, Patricia A. Russell, Ursula M. Ruston, [illegible] Salmon, W. M. Sare, D. M. M. Sayers, Margaret Schafran, J. Schen, J. E. Scriven, William Sewell, F. C. Shelley, P. M. hore, H. L. Silver, I. H. S. Silver, G. B. Skinner, A. C. R. Skynner, G. Slater, G. I. Small, A. J. Smith, B. A. Smith, D. C. Smith, C. Smith, J. D. Somper, Anthony Spellman, E. C. Spencer, W. Sprigge, R. M. Stanford, Mary J. Starbuck, A. E. Stevens, C. J. Stoke, A. E. Strigner, G. A. Stroud, Mary W. Sturges, H. Sullivan, M. W. Swallow, Mary T. Taylor, G. G. Thomas, E. M. Thomas, J. D. Thomas, R. E. M. Thompson, H. H. Thomson, J. Todd, J. N. Todd, Molly E. Towell, Peter Train, P. E. Tucker, E. Tunstall, Annemarie D. Tupper, Prudence Valentine, G. W. addy, P. O. Wakelin, Phyllis M. Wallington, R. W. Wallis, oanna M. Ward, C. H. W. Warne, L. P. E. Watson, M. B. Watts, S. Wells, G. F. Westcott, H. R. Whitaker, Ingeborg R. Wiernik, eonard Williams, M. C. Williams, J. H. Willis, H. J. W. Willson, M. Wilson, Victor Wilson, K. J. Wing, Frank Winston, P. A. oodbridge, Susannah M. Woodcock, W. A. A. Woodruff, C. I. oolf, Dorothy E. Wright, P. A. C. Wright, J. K. N. Yearsley, C. Young, H. L. Young, Alec Zisserman, P. A. Zorab.

ociety of Apothecaries of London

The following diplomas have been granted:

L.M.S.S.A.—A. Levinsohn, R. E. H. Jones, F. D'U. Burgess, E. Sharp, E. J. Stacey, J. A. Marais, H. C. Cunningham, T. J. tanton, A. H. Barker, K. G. Somers-De Haney, G. M. Gaskell, P. Burns, H. St. J. Mansbridge, M. C. Shah, W. R. Shanks, D. France, M. Kassab, J. W. Leach, D. M. Carter, R. C. H. adell, I. A. Campbell, R. E. Fryer, A. G. Hilmy, J. P. Turner, J. H. Cheong, L. J. Miller, J. H. Kerr, C. M. Stafford, P. W. eston, C. P. B. Brook, V. S. Nicholson, P. G. Woolf, G. F. Lambert-orter, P. F. Knight, L. A. Lees.

M.M.S.A.—M. I. Cookson, G. E. Peters, S. E. Sash, E. N. S. 'Arcy.

D.I.H.—W. F. Felton, D. G. R. Fox.

Royal College of Obstetricians and Gynæcologists

At a meeting of the council held on May 24, with Dame Hilda Lloyd, the president, in the chair, the following were elected to the council:

As representatives of the fellows—O'Donel Browne, Dublin; G. F. Gibberd, London; H. J. Malkin, Nottingham; S. W. Maslen-Jones, Wolverhampton.

As representatives of the members—Gavin Boyd, Belfast; L. B. Patrick, Sheffield.

The following were admitted to the fellowship:

Yeshwant Narayen Ajinkya, A. W. Andison, Alice J. M. T. Barnes, C. W. F. Burnett, W. D. A. Callam, G. P. Charlewood, Samuel Davidson, Richard de Soldenhoff, A. B. Evans, D. B. Fraser, H. F. P. Grafton, N. McA. Gregg, G. G. Lennon, W. A. Liston, Ruvin Lyons, Hugh McLaren, R. F. Matters, B. E. Meek, H. K. Porter, P. G. Preston, D. C. Racker, G. W. Robson, J. W. Schabort, G. G. L. Stening, S. L. Townsend, J. C. Whyte, R. J. Wotherspoon.

The following were admitted to the membership:

E. McL. Barbour, Caroline D. Baugh, R. M. C. G. Beard, D. C. G. Bracken, K. McL. Crocker, Victor Drosso, M. P. Durham, James Elstub, Bruce Eton, M. R. Fell, Hugh Ferguson, C. M. Flood, F. G. Geldenhuys, Vinayak Balvant Gokhale, P. F. C. Jackson, A. I. I. Klopper, J. B. Lawson, Sarah Lehane, A. D. McIntosh, Declan Magner, Declan Meagher, A. P. B. Mitchell, Nathan Moss, T. R. Nelson, Margaret B. Noble, C. B. Oxner, John Price, H. I. Schmilg, W. H. D. Scotland, R. S. L. Stafford, Joan E. Storey, Ewen Sussman, J. S. Tomkinson, F. L. A. Vernon, Joseph Ward, P. P. Wium.

Ulster Pædiatric Society

Dr. Samuel Barron has been elected chairman of this society for 1952–53.

Pneumoconiosis Research Unit, Cardiff

Dr. John Gilson, the present assistant director, is to succeed Dr. Charles Fletcher as director of this Medical Research Council unit in October.

Dorothy Platt Lecture

Prof. D. W. Smithers will deliver the first Dorothy Platt memorial lecture on Tuesday, July 1, at 4.30 P.M., at King's College Hospital Medical School, Denmark Hill, London, S.E.5. He will speak on Progress in the Treatment of Breast Cancer.

Society for the Study of Fertility

A meeting of this society will be held on Friday and Saturday June 27 and 28, in the meeting-house of the Zoological Society of London, Regent's Park, N.W.1. Further particulars may be had from Dr. G. I. M. Swyer, hon. secretary of the society, University College Obstetric Hospital, Huntley Street, W.C.1.

Presentation to Lord Boyd-Orr

On May 29 at a reception at the House of Lords, Lord Haden-Guest on behalf of the contributors presented to Lord Boyd-Orr, F.R.S., a bound copy of the book of essays *Four Thousand Million Mouths* which was edited by Mr. F. Le Gros Clark and Mr. N. W. Pirie, F.R.S.

French Courses in Research Techniques

The Centre National de Coordination des Études et Recherches sur la Nutrition et l'Alimentation is organising summer schools (limited to a few members) on (1) paper partition chromatography of amino-acids and peptides, and paper electrophoresis of proteins; (2) methods for the microbiological assay of certain vitamins; and (3) lactic bacteria of milk and milk products. Particulars may be had from the Scientific Office, French Embassy, 22, Wilton Crescent, London, S.W.1.

Conference of Adoption Societies

Closer liaison between adoption societies and the children's departments of local authorities was suggested by Mr. E. Ainscow, principal children's officer of the London County Council, at the Standing Conference of Societies Registered for Adoption, held in London on May 26, which was attended by about 250 child-welfare workers, from all over the country. The Hon. Mrs. Geoffrey Edwards, chairman of the standing conference, said that a beginning had been made by the decision to coöpt a "speaking observer" from the Association of Child Care Officers to the executive committee of the Standing Conference. The conference had also discussed the need for the better regulation of third-party adoptions and direct placements of children by their own mothers, and for hostels where a mother could take her baby and get a job to support them both, instead of letting her child be adopted.

National Association for Mental Health

The Clothworkers' Company have given the association £500 in memory of King George VI, asking that it should be used "for the relief of poverty in general (particularly where combined with old age and affliction)."

A New Sign Language

On Wednesday, June 11, at 5.30 P.M. at the Wellcome Research Institution, Euston Road, London, N.W.1, Sir Richard Paget, F.INST.P., will give a demonstration, including a sound film, of a new sign language which he has devised. Otologists and those interested in the education of the deaf are invited to attend.

Blood-transfusion Award

The committee of the Oliver Memorial Fund make an award from this fund (£50) for original work or services in connection with blood-transfusion. Applications or communications drawing attention to suitable candidates should be sent before July 31 to the hon. treasurer, Mr. F. W. Mills, c/o National Provincial Bank, Holborn Circus, London, E.C.1.

Symposium on Suicide

A joint meeting of the research and clinical section of the Royal Medico-Psychological Association and the British Sociological Association is to be held at the London School of Economics, Houghton Street, London, W.C.2, at 8 P.M., on Friday, June 13, when Prof. M. Ginsberg D.LIT., will speak on the Sociological Aspects of Suicide and Dr. P. Sainsbury on Researches into Suicide in the London Boroughs. Dr. E. Stengel will open the discussion.

The Health Service Charges

In a speech at the Constitutional Club in London reported in the *Times* of May 31 Mr. Iain Macleod, the Minister of Health, said that though he would make no cheap or easy promises he would watch the effect of the new charges on the queues at the surgery and the outpatients' department, on the recruitment of dentists, particularly to the school dental service, on the relationship to the cost of the service, and the relationship of the cost of the service itself to the whole field of Government expenditure. "Charges," he added, "there must certainly be now and for some time to come, but the Government in this Act do not declare that charges must or should remain a permanent part of the National Health Service."

Mr. H. L. Jackson, chairman of H. K. Lewis & Co., medical publishers, London, died on May 29 at the age of 82. He came to the firm as an assistant in 1888, and he became a partner in 1905.

Mr. St. J. D. Buxton has been appointed an honorary consultant in orthopædic surgery to the Ministry of Pensions.

Appointments

ACRES, G. C., M.R.C.S.: M.O., London Transport Executive.
COOPER, R. S., M.B. Lond.: asst. county M.O., Hertfordshire.
DAVIDSON, A. G., M.B. Aberd.: appointed factory doctor, Tongue district, Sutherland.
JACK, J. D., L.R.C.P.E.: appointed factory doctor, Helensburgh district, Dumbarton.
JACKSON, G. A., M.B., B.SC. Dubl.: anæsthetist registrar, South Devon and East Cornwall Hospital, Plymouth.
MACGREGOR, D. F., M.A., B.M., B.SC. Oxfd, D.P.M.: whole-time asst. psychiatrist, Carlton Hayes Hospital, Narborough, Leicestershire.
MYATT, CONSTANCE, M.B. Birm., D.P.H., D.I.H.: M.O., London Transport Executive.
*TAYLOR, SELWYN, M.A., M.CH. Oxfd, F.R.C.S.: surgeon, King's College Hospital, London.
THOMAS, G. F. H., M.R.C.S., D.P.H.: M.O. (S.H.M.O.), St. David's Hospital, Cardiff.

*Amended notice.

Manchester Regional Hospital Board:

CURRY, JOHN, M.D. Manc.: consultant dermatologist, Oldham, Ashton, and Stockport hospital centres, and the Manchester and Salford Hospital for Skin Diseases.
DICKSON, W. P. G., M.B. Glasg., M.R.C.O.G.: consultant obstetrician/gynæcologist, Lancaster and Kendal hospital centre.
DUNCAN, P. R., M.B. Manc., M.R.C.P.: consultant physician, Victoria Hospital, Blackpool.
WARD, R. L., M.D. Lond., M.R.C.P.: consultant chest physician, Blackburn and district hospital centre.
WILSON, JOHN, M.B. Leeds., D.M.R.D.: asst. radiologist, Barrow and Furness hospital centre.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Diary of the Week

JUNE 8 TO 14

Monday, 9th

INSTITUTE OF CHI ospital for Sick Children
Great Ormond
5 P.M. Prof. Alfr fant Mortality.
ROYAL EYE HOSPIT S.E.1
5 P.M. Dr. T. H. and the Eye.
INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark S.E.5
5.30 P.M. Dr. Denis Hill: Lecture-demonstration.

Tuesday, 10th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. G. McC. Wyburn: Congenital Defects of the Ant Abdominal Wall. (Arris and Gale lecture.)
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hos Medical School, W.2
5 P.M. Dr. E. Jawetz (California): Antibiotic Synergism Antagonism.
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Sections of Psychiatry and Anæsthetics.* Dr. Au Ferguson, Dr. A. W. Edridge: New Muscle Relax in E.C.T.
INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle St W.C.2
5.30 P.M. Dr. P. M. F. Bishop: Skin Changes in Relatio Endocrine Disturbances.
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P.M. (Hammersmith Hospital, Ducane Road, W.12.) D Hilda Lloyd, F.R.C.O.G.: Gynæcological Sequelæ Labour.
ROYAL EYE HOSPITAL
5 P.M. Dr. A. C. Cunliffe: Bacteriology of the Eye.
SOCIETY FOR THE STUDY OF *ADDICTION*
8 P.M. (Westminster Medical School, Horseferry Road, S.W Dr. P. O. Wolff: Activities of the World Health Orga tion in Drug Addiction. (Kelynack lecture.)

Wednesday, 11th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, V
11.45 A.M. Medical clinical-pathology Conference.
2 P.M. Dr. R. R. Race, F.R.S.: The Nine Human Blood-g Systems.
INSTITUTE OF CARDIOLOGY
5 P.M. (1, Wimpole Street, W.1.) Dr. William Evans: (phageal Contraction and Cardiac Pain. (St. Cyres lect
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Medical Mycology—Trichoph Infections.

Thursday, 12th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Prof. John Crofton: Pneumonia.
ROYAL SOCIETY OF MEDICINE
5 P.M. *Section of Ophthalmology.* Prof. Sven Larsson (Lu Clinical Problems Receiving Special Attention at Ophthalmic Clinic, The University, Lund.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Cor S.W.1
5 P.M. Dr. J. Hamilton Paterson: Neurology lect demonstration.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. O. Oliver: Pathology—Reticuloses.
MIDDLESEX COUNTY MEDICAL SOCIETY
8 P.M. (Central Middlesex Hospital, Park Royal, N.W. Mr. J. S. MacVine, Dr. E. S. Skene, Dr. Dorothy Tayl The Maternity Services.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) *Sir Geof* Jefferson, F.R.S.: Brain-stem Mechanisms and t Influence on Survival in Diseases of the Brain.

Friday, 13th

POSTGRADUATE MEDICAL SCHOOL OF *LONDON*
11.15 A.M. Surgical clinical-pathology conference.
2 P.M. Mr. O. S. Tubbs: Surgery of the Patent Ductus.
ROYAL SOCIETY OF MEDICINE
10 A.M. (Manchester Royal Infirmary.) *Sections of Laryngol and Otology.* Prof. Theo Walsh (St. Louis): Spe Audiometry. Mr. T. S. Littler, D.SC., Mr. J. J. Knig Miss P. H. Strange: Bone-conduction. Mr. Ralph Naunt Mr. Peter Denes: Use of Masking in Audiometry.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. H. J. Wallace: Congenital and Late Devel mental Abnormalities.

Saturday, 14th

ROYAL SOCIETY OF MEDICINE
10 A.M. (Manchester Royal Infirmary.) *Sections of Laryngol and Otology.* Dr. De Graff Woodman (New York): Bilate Abductor Paralysis—Past Eight Years' Experience wi the Open Approach to Arytenoidectomy. *Prof. Vic* Lambert: Mixed Salivary Tumours of the Up Respiratory Tract. Mr. Kenneth Harrison: Buccal a Pharyngeal Ulcerations of Virus Origin. Mr. H. Bedford Russell, Mr. Leslie Wright, Mr. G. Ashcrof Significance of Alveolar Osteitis in Rhinology.
SOUTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY
11 A.M. (Eversfield Chest Hospital, St. Leonards, Suss Dr. E. A. Wood: The Catarrhal Child.

PHYSIOLOGICAL PRINCIPLES UNDERLYING THE TREATMENT OF HIGH DIASTOLIC ESSENTIAL HYPERTENSION BY THIOCYANATES AND SYMPATHECTOMY*

LOYAL DAVIS
M.D. Northwestern
PROFESSOR OF SURGERY, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO

FOUR periods encompass our present knowledge of hypertension: (1) in the beginning Richard Bright attributed the cardiac hypertrophy of patients with renal disease to changes in the blood which he believed capable of increasing the work of the heart; (2) the second period was influenced by the introduction of the sphygmomanometer by von Basch and the contributions of Allbutt, Suchard, Janeway, and Volhard and Fahr; (3) in 1934 Goldblatt reproduced hypertension experimentally by partial occlusion of the renal arteries; and (4) at present the theory of the general adaptation syndrome and the diseases of adaptation, including hypertension, influence investigation and may be traced back to the broad general concept of vasomotor tone and balance established by Anrep, and Cannon's principles of homeostasis.

This disease—the prealbuminuric stage of chronic Bright's disease, the latent arteriosclerosis of von Basch, the hyperpiesia of Allbutt, the pre-sclerosis of Suchard, the hypertensive cardiovascular disease of Janeway, the benign and malignant sclerosis of Volhard and Fahr—is most widely known in the United States as essential hypertension.

ÆTIOLOGY

Those who support the renal theory of pathogenesis contend that essential hypertension is a disease of the kidneys. The adherents of a neurohumoral mechanism suppose (1) that continued arterial hypertension is one sign of the presence of essential hypertension, (2) that this sign often precedes any recognisable organic changes, and (3) that disorders of function in the neuropsychic, endocrine, and renal systems may cause the manifestations of the disease.

From a large number of investigations there has developed a hypothesis which states that the immediate cause of experimental hypertension is related to renal ischæmia, and that renin and hypertensin are probably the substances which cause the blood-pressure to rise. There seems to be no doubt that a pressor and vasoconstrictor substance is present in the renal venous blood of animals made hypertensive by constricting the renal arteries. This substance has been named *renin*, a protein with no vascular action of its own but with enzymatic properties. Its pressor and vasoconstrictor activities depend on *hypertensin*, a polypeptide of relatively low molecular weight formed by the interaction of renin with *hypertensinogen* and destroyed by *hypertensinase*. Hypertensinogen, a globulin present in the blood-plasma, is formed in the liver and disappears almost completely from the systemic blood-stream in untreated adrenalectomised dogs.

CLASSIFICATION

Essential hypertension may be divided into six clinical groups:

(1) The *fluctuant* type, which represents a large proportion of the early cases of hypertension observed usually in the 'teens or early twenties, has often been described as adolescent hypertension, and is not associated with renal disease. It is usually asymptomatic and is only discovered as the result of a routine physical examination. During these early years it is impossible to tell whether the disease will remain quiescent, progress into one of the other clinical types, or, in some cases, disappear entirely. So long as the ætiology cannot be determined, associated renal disease is not discovered, and the patient remains asymptomatic, it is questionable whether any therapy should be instituted. However, in my experience these patients uniformly respond well to thiocyanates.

(2) The *plethoric* type is usually seen in the typical "business man" with hypertension. The patient is energetic, active, and overweight, and may have distressing symptoms, particularly headaches, vertigo, and anginoid distress associated with cardiovascular disturbances. The hæmatocrit is usually more than 50%, the red-cell count higher than 5,000,000 per c.mm., and the erythrocyte-sedimentation rate (E.S.R.) 1–5 mm. or less in 1 hour (Wintrobe). Provided that these patients do not have associated irreversible renal disease, the maintenance of a therapeutic blood-cyanate level will lead to rather prompt relief of the hypertensive symptoms and gradual diminution of, first, the systolic and, later, the diastolic pressures. During the first few months' treatment the hæmatocrit will drop to 45% or less, and the E.S.R. will rise to 10–15 mm. in 1 hour. This represents a definite change in the hæmogram resulting from a thiocyanate effect on the red-cell count and on blood viscosity.

(3) *Menopausal* hypertension is one of the most common types and corresponds in many respects to the plethoric type of hypertension in the male. It is accompanied by numerous severe symptoms of hypertension superimposed upon those associated with the menopause. However, a high hæmatocrit and a low E.S.R. are not often seen, but the blood-cholesterol level is likely to be raised. The hypertensive, as well as the menopausal, symptoms can often be controlled by œstrogenic therapy and sedation alone, but the blood-pressure, which is not affected by these measures, will often respond to thiocyanate therapy. The menopause is not, in itself, a cause of essential hypertension, but it may exaggerate the symptoms of a pre-existing or coincidental hypertension in patients with only a moderately raised blood-pressure. It has long been observed that, if the patient can be brought safely through the period of menopausal symptoms, be it five or fifteen years, the hypertension may subsequently burn itself out.

(4) The *high diastolic* type of hypertension, as seen in the male most often between the ages of 35 and 50, represents the most severe type of essential hypertension. It indicates either a premalignant phase of hypertension or a rapidly progressing type of essential hypertension leading to heart-failure or a cerebral vascular accident within five years. Unlike the female in this same age-group with a severe high diastolic pressure, the male does not tolerate an increased blood-pressure for very long. These patients may not respond well to the thiocyanates except for a relatively short time; and if they do show some blood-pressure lability and some response to the thiocyanates, though it is temporary, they have been subjected to sympathectomy before the onset of renal and cardiac failure or malignant hypertension.

(5) *Arteriosclerotic* hypertension, usually seen in its early phases between the ages of 50 and 60, is characterised by relatively high systolic and relatively low diastolic blood-pressures. Its course well represents the protracted and benign nature of some cases of hypertension, although it is often accompanied by cerebral symptoms of headaches, vertigo, and tinnitus, and even by symptoms of left ventricular failure. The disease itself is not severe and is compatible with a rather long and useful life. Some patients respond very well to small doses of thiocyanates, but they should be observed very carefully to avoid a rapid drop in blood-pressure.

(6) *Malignant* hypertension, which may occur in any age-group with a clinical course which rapidly progresses to death, manifests itself by severe progressive generalised necrotising arteriolar disease and renal failure with severe hypertensive symptoms, including convulsions and coma. The disease shows no response to thiocyanates or any other medicinal therapy. A patient with any of the previous types of hypertension may suddenly and unpredictably enter the malignant phase of essential hypertension, but it is most likely to happen in the group with high diastolic blood-pressure.

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* Abridgement of a Litchfield lecture given at Oxford University on Oct. 10, 1951.

INDICATIONS FOR SYMPATHECTOMY

I have done sympathectomy only on patients whom I classify as having the high diastolic type of hypertension. Also, I restrict my choice to those in this group who have been given a thorough therapeutic trial with the thiocyanates and have proved resistant to that drug. That is to say, the patients' diastolic and systolic blood-pressures and their symptoms cannot be improved by blood-cyanate levels below those which produce gastro-intestinal symptoms.

Another indication for the choice of patients for sympathectomy has been that they should have a labile blood-pressure shown by pressor and depressor tests. None of these tests have ever given any information of the character or extent of the response which might be expected after sympathectomy. Among the general considerations which constitute surgical indications are that (1) the patients have no evidence of chronic glomerulonephritis or pyelonephritis; (2) no significant peripheral vascular sclerosis is present; and (3) the clinical course is progressive but not entering the malignant stage of hypertension.

EFFECT OF THIOCYANATES

Simultaneously, I have been engaged in the experimental surgical laboratory with the problem of hypertension. We can make dogs hypertensive by partially constricting their renal arteries, as described by Goldblatt (1948). The blood-chemistry and other laboratory findings in these dogs are similar to those in patients. It is possible to reduce the blood-pressure of these dogs by raising the blood-thiocyanate level. When thiocyanates are discontinued and the blood-cyanate level reaches zero, the blood-pressure returns to its original high level. The only observed effect of the administration of thiocyanates on the viscera is a fatty infiltration of the liver, with preservation of the cell nuclei. This change in the liver is reversible when the thiocyanates are discontinued.

COMBINED TREATMENT WITH SYMPATHECTOMY AND THIOCYANATES

As often happens in the pursuit of the solution of a problem, a chance observation may change the entire direction of the investigation, or the conclusions therefrom. There had been under medical therapy a man with progressive hypertension of the high diastolic type. His blood-pressure had not been decreased by the carefully controlled administration of large doses of thiocyanates, and he showed evidence of gastro-intestinal intolerance of the drug. He sought advice elsewhere, and bilateral sympathectomy was done. He did well for two or three weeks after the operation, but after that his blood-pressure resumed its former levels and his symptoms recurred. He returned for further care, and in desperation was again given thiocyanates. Much to my surprise, the systolic and diastolic pressures were significantly decreased with a lower blood-cyanate level than had been possible before the operation, and the patient improved steadily. Similar observations have been made repeatedly.

I believe that sympathectomy alone is not successful in permanently reducing the blood-pressure or in improving the symptoms and clinical course in the high diastolic type of hypertension, regardless of the extent of the operation. I have done thoracic sympathectomy from the ninth to the twelfth ganglia inclusive, with resection of the splanchnic nerves, with and without inclusion of the first three lumbar ganglia and chain; I have removed the splanchnic nerves alone; and I have removed the thoracolumbar sympathetic chain as high as the fourth thoracic ganglion and as low as the third lumbar ganglion, with resection of the splanchnic nerves.

RÔLE OF ADRENAL CORTEX

The physiological explanation of the observation that patients who were resistant to the thiocyanates before sympathectomy, and in whom sympathectomy alone was without effect, responded favourably postoperatively at a lower blood-cyanate level, was sought in the laboratory and clinic.

Pressor substances have been found in the blood of patients with essential hypertension and in dogs with experimental renal hypertension. These pressor substances cannot be formed without the participation of the liver and the adrenal glands. Recent work points to the adrenals as the main factor in the entire humoral mechanism involved.

It is known that sympathectomy depresses the function of the adrenal glands and deprives the laboratory animal of its ability to react completely to the stimuli of an emergency situation. Since the thiocyanates, combined with sympathectomy, give better results in the treatment of hypertension than does either method alone, in both man and dogs, experiments were made to determine if any evidence could be found which might indicate that the thiocyanates produce a sustained depressor action by further inhibiting the function of the adrenal gland. This would imply that the thiocyanates act on the adrenal cortex, a hypothesis heretofore unconsidered.

The rôle of the adrenal cortex in the adaptation of the body to noxious agents is widely accepted. Under such conditions the adrenal glands undergo morphological and cytochemical modification. Lipid substances which stain with Sudan III are distributed in a definite pattern within the three layers of the adrenal cortex: the outer zona glomerulosa, the middle zona fasciculata, and the inner zona reticularis. It is generally accepted that stimulation of adrenal cortical activities increases these lipids, and a reduction of cortical activity decreases them. Although a complete parallelism may not exist between the sudanophilic lipid granules of the three layers of the adrenal cortex, there are many reasons to believe that they are identical with specific ketosteroids. This cytochemical method of following the function of the adrenal gland is an accurate one.

In experiments on rats injections of potassium thiocyanate 10–15 mg. per kg. of body-weight were given, and at various intervals histological sections of the adrenal cortex were studied for their lipid content. The lipid content was depleted in all the layers of the adrenal cortex, more especially in the zona glomerulosa; this effect closely followed the blood-thiocyanate levels.

The same type of experiments were repeated in dogs, sodium thiocyanate being given intravenously and potassium thiocyanate by mouth, with similar histological findings in the cortex of the adrenal glands. In addition to depleting the amount of lipid in the adrenal cortex, the intravenous administration of thiocyanates to dogs produces depression and lassitude, and the blood-chemistry changes resemble those found in adrenalectomised dogs. In this group of experiments it was shown also that the blood-thiocyanate level could be raised to a high point by administering the drug intravenously, whereas an attempt to reach the same level by administering the drug by mouth was followed by gastro-intestinal symptoms. From these observations I believe that the symptoms caused by the administration of thiocyanates by mouth in patients are not due to the toxic effects of the drug but simply to gastro-intestinal intolerance.

Biopsy studies of the adrenal cortex of patients with essential, or high diastolic, hypertension submitted to sympathectomy were made before and after thiocyanate therapy. There were changes in the distribution of lipids within the different layers of the cortex which were similar to those found in the experiments with thiocyanates on normal dogs, and varied when the blood-thiocyanate levels were zero and when they were raised. The size, distribution, and amount of these lipid granules in the adrenal cortex of a patient with essential hypertension who had never received thiocyanates, compared with the depleted appearance in the adrenal cortex of the same patient with a high blood-thiocyanate level, was striking.

Similar experiments were made on dogs in which hypertension had been experimentally produced by partial constriction of the renal arteries. Histological studies were made of the adrenal cortex in these dogs before and after sympathectomy and with the blood-thiocyanate level at zero and at a high level. The results paralleled those found in man.

That the liver plays a rôle in hypertension has been suggested by many investigators, and to it has been assigned the rôle of the production of a vasodepressor substance which is normally in balance with a vasopressor substance originating in the kidney. It has been demonstrated that the level of hypertensinogen in the plasma is maintained by production in the liver, and, since the decrease in hypertensinogen is described only in some cases of experimental acute liver injury, experiments were made to produce low-grade hepatic lesions in an attempt to inhibit the formation of hypertensinogen.

Partial occlusion of the portal vein led to a fall in the systemic blood-pressure of dogs with experimental renal hypertension. To obtain a lasting reduction of the blood-pressure in these dogs, the partial occlusion of the portal vein must be sufficient to produce histological evidence of mild chronic insufficiency of the liver, represented microscopically by fatty infiltration of the liver-cells, which, however, maintain their well-preserved nuclei. The histological appearance is similar to that seen in the liver after the administration of thiocyanate.

The systemic blood-pressure was not reduced immediately after partial occlusion of the portal vein. This suggests an indirect, rather than a direct, participation in the mechanism which controls the systemic blood-pressure. There was considerable depletion of lipids in the zona fasciculata and the zona reticularis, but with relatively little or no loss in the zona glomerulosa, of the adrenal cortex of these dogs. The granules in the zona fasciculata and zona reticularis were consistently smaller and uniform in size. There were none of the large coalescing particles of lipid found in the adrenal cortex of the normal dog. After the injection of protoveratrine, which lowers the blood-pressure in laboratory animals over an extended period, histological examination of the adrenal cortex showed no change in the distribution of the lipid granules such as occurs with thiocyanates.

The changes in distribution of the lipids in the adrenal cortex in normal dogs, hypertensive patients, and dogs with experimental hypertension, when the blood-thiocyanate level is elevated, are similar. They suggest that the thiocyanates have a particular affinity for inhibiting the function of the adrenal cortex.

It is known that sympathectomy alone inhibits the function of the adrenal glands. However, in patients with the high diastolic type of essential hypertension, sympathectomy alone does not permanently affect the blood-pressure or change the course of the disease. Removal of the sympathetic innervation of the adrenal gland, when it is effective in hypertensive patients, lowers the systolic pressure first and the diastolic pressure more slowly. Since the functional innervation of the adrenal cortex is not yet known, it might be assumed that sympathectomy leads to a decrease of the medullary output of adrenaline. Since adrenaline stimulates the formation of the adrenocorticotropic hormone, which in turn stimulates adrenal cortical function, it may be suggested that adrenal cortical function will be reduced after denervation of the adrenal medulla.

Since thiocyanates deplete lipids in the layers of the adrenal cortex in normal dogs, in patients with a high diastolic type of hypertension, and in dogs with experimentally produced hypertension, it would seem that depletion of these cortical lipids is in part responsible for the fall in blood-pressure. It has been shown that with a drop in the blood-thiocyanate level there is restoration of lipid material to the previously depleted zona glomerulosa, a return to the normal pattern of lipid distribution in the zona fasciculata, and a return of the systolic blood-pressure to the original high level in experimentally hypertensive dogs. Consequently, reduction in adrenal cortical function by sympathetic denervation of the adrenal medulla and by the administration of thiocyanates may lead to a more effective lowering of blood-pressure than can be accomplished by either alone.

The lipid granules in the adrenal cortex of hypertensive dogs are depleted after partial occlusion of the portal vein just as they are after the administration of thiocyanates; but the depletion is well marked in the zona fasciculata and zona reticularis while the zona glomerulosa shows only a relative depletion. It may be postulated that, in addition to a decrease in the production of hypertensinogen by the liver, there is an increase in a substance which depletes the lipid substances of the fasciculata and reticularis layers of the adrenal cortex. The result is a lowering of the systemic blood-pressure.

SUMMARY

Many patients with the high diastolic type of essential hypertension can have their hypertensive symptoms controlled by the administration of thiocyanates to make them socially and economically independent; but some of these patients are resistant to thiocyanate therapy, and others, who originally responded to thiocyanates later become resistant.

Patients who are resistant to thiocyanate therapy responded to it after sympathectomy. Sympathectomy alone has no permanent effect on the blood-pressure or the clinical course of patients with the high diastolic type of hypertension, regardless of the extent of the operation.

The blood-pressure of hypertensive dogs can be reduced by the administration of thiocyanates. The blood-thiocyanate level in patients and dogs can be increased by administering the drug intravenously, thus avoiding the symptoms of gastro-intestinal intolerance.

Biopsy specimens of adrenal cortex taken, before and after the administration of thiocyanates, from patients with essential hypertension show that the administration of the thiocyanates causes a definite depletion of the sudanophilic lipid granules in the three layers of the adrenal cortex. In dogs with experimental hypertension the administration of thiocyanates similarly depletes the lipid granules in the layers of the adrenal cortex, and there is a rapid return to normal when the thiocyanates are withdrawn.

It is suggested that the thiocyanates depress the function of the adrenal glands and produce changes in the blood chemistry, and symptoms in dogs and man, similar to those of an adrenalectomised animal. The thiocyanates inhibit the function of the adrenal cortex and in this manner help to restore the balance between the depressor and pressor mechanisms controlling the blood-pressure.

There is evidence which supports the hypothesis of a dual mechanism in the control of the blood-pressure in normal people—i.e., the depressor mechanism extends from the function of the liver, and the pressor mechanism from the functions of the adrenal glands. The production of a mild chronic insufficiency of the liver by partial occlusion of the portal vein reduces the blood-pressure in dogs with experimental renal hypertension. *In such* dogs there is depletion of the lipid granules in the adrenal cortex, but the distribution of the pattern is different from that found after the administration of thiocyanates.

It is suggested that in hypertensive patients there is an imbalance between the normally existing pressor and depressor mechanisms represented respectively by the adrenal glands and the liver. Clinically, the goal of therapy should be to restore this balance in the hypertensive patient. The administration of thiocyanates inhibits the pressor mechanism by their action on the adrenal cortex, particularly its lipid granules. By decreasing the function of the adrenal medulla sympathectomy augments the action of the thiocyanates in inhibiting the pressor action of the adrenal cortex.

BIBLIOGRAPHY

Davis, L., Barker, M. H. (1938) *Ann. Surg.* **107**, 899.

— — (1939) *Ibid*, **110**, 1016.

— — (1941) *J. Lab. clin. Med.* **26**, 658.

— Lindberg, H. A., Treger, N. Y. (1948) *Ann. Surg.* **128**, 770.

— Tanturi, C. A. (1951) *Arch. Surg.* **62**, 325.

— — Tarkington, J. (1950) *Ann. Surg.* **132**, 394.

— Tarkington, J., Anderson, R. K. (1951) *Ibid*, **133**, 867.

Goldblatt, H. (1948) The Renal Origin of Hypertension. Springfield, Ill.

Green, R. O., Deane, H. W. (1949) *Ann. N.Y. Acad. Sci.* **50**, 596.

Lindberg, H. A., Wald, M. H., Barker, M. H. (1941) *Amer. Heart J.* **21**, 605.

SEALED DRAINAGE OF WOUNDS

M. D. SHEPPARD

M.B. Lond., F.R.C.S.

SURGEON TO THE CHELMSFORD HOSPITAL GROUP

CHEMOTHERAPY and antibiotics have reduced the need for drainage of wounds, and modern surgical practice dictates the closure of wounds whenever possible.

This reluctance to leave a communication between the outer world of microbes and the inner recesses of the body is readily understandable. But nevertheless, the avoidance of drainage has not always been guided by sound principles, and, in hoping to prevent secondary infection, this policy of undue optimism has at times led to complications, which have prolonged the patient's convalescence and even jeopardised his survival.

The reasons for the present aversion to drainage are:

(1) Leakage from an open wound requires frequent attention, with consequent repeated exposure to an infected ward atmosphere and the organisms of the dressers. The probability of harm from secondary infection outweighs the advantages of clearing the depths of the wound of sterile or even infected effusions.

(2) Healing is delayed, and scars are weakened. Adhesions are more common and firmer after the use of indwelling foreign bodies with a smouldering secondary infection.

(3) Open drainage necessitates the use of bulky dressings, which are expensive and limit the patient's activity, confining him to bed when he could otherwise be up and about.

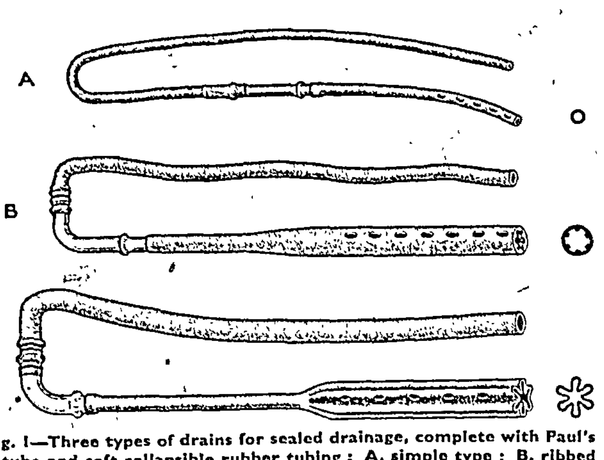

Fig. 1—Three types of drains for sealed drainage, complete with Paul's tube and soft collapsible rubber tubing: A, simple type; B, ribbed type; C, corrugated type.

(4) The discharges are seldom completely absorbed by any type of dressing and usually soil garments and bed-clothes, thus further contaminating the ward and leading to heavy laundry charges.

(5) Wounds, sutures, and surrounding skin remain sodden, loosening the dressing fixatives, and all too often exposing the wound to the patient's fingers and soiled clothes.

A common and disturbing sight is the uncovered lower end of a suprapubic wound draining on to the genitalia and buttocks. Any surgeon who takes the trouble to inspect his wounds before ward dressing-time will certainly notice that the lower abdomen is often bared, through riding up of the many-tail bandage and loosening of adhesive strapping. Far too much valuable nursing time must be spent on such patients to keep their open drained lesions safe and clean.

Yet the greater the amount of discharge, the greater is the need for its clearance. This can be achieved without any of the foregoing objections.

THE SEALED DRAINS

Messrs. William Warne & Co. have prepared for me three types of latex rubber tubes, which have been put to extensive tests with entirely satisfactory results.

The simplest sealed drains can be fashioned from a length of ordinary latex tubing made in various gauges (fig. 1A). The material is soft, pliable, and non-irritant. It stands frequent boiling, and the same tube can be used over and over again.

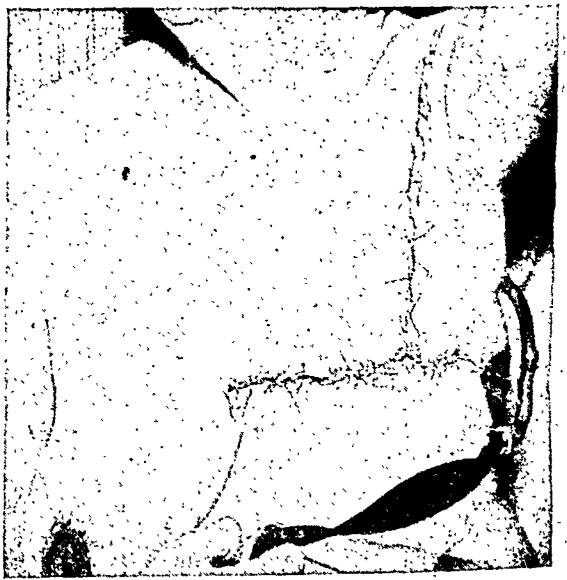

Fig. 2—Radical mastectomy wound with sealed type-A drain passed through small separate incision in posterior axillary line, and with collecting end of drain fixed with catgut suture in apex of axillary space. Sutures and drain are removed on twelfth postoperative day.

The collecting end of the drain is perforated at regular intervals, care being taken to confine the holes to that part of the tube deep to the wound margins. To the delivery end, projecting well beyond the wound dressing, is fixed a Paul's tube to which is firmly secured a good length of thin-walled collapsible rubber tubing. This simple combination has proved adequate for the drainage of wounds of moderate size and depth in which the discharge is free from large clots.

The second type of latex rubber drain (fig. 1B) is a wide-bore tube with soft thin walls reinforced by internal ribs, which ensure patency even when the tube is bent and compressed. The collecting end is liberally perforated and serves well for the drainage of large and deeply placed cavities, such as the subphrenic and pleural spaces and the pouch of Douglas.

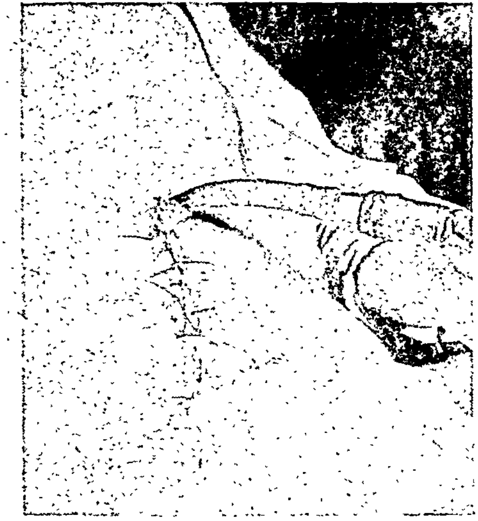

Fig. 3—Cholecystectomy and choledochotomy wound with ribbed tube draining gall-bladder bed. In spite of much leakage of bile after removal of T-tube, wound was kept dry and drain was not removed until common bile-duct had closed. Patient remained ambulant.

The third type is no doubt the most effective but is costly and difficult to make (fig. 1c). The collecting end is expanded to form a corrugated cylinder; its grooves are freely perforated, and its large collecting area carries the discharges to the delivery tube, around which the wound can be easily sealed. Where highly efficient drainage of clots, fibrin, and inspissated pus from a large cavity is essential, this third model will function without fail.

The objection may be raised that the corrugated collecting end is too bulky and will cause discomfort and foreign-body reaction, but we usually leave it in the body until the discharge is minimal, often as long as fourteen days, and it seems to be well tolerated, and its removal is usually followed by prompt healing.

METHOD OF USE

To ensure success with a sealed drain, the tube must be carefully placed and proved to be working before the wound is firmly closed beyond the most distal collecting hole.

The tube is next securely fixed to the skin with a clove hitch, which grips it tightly and resists any pull. A stitch must not be passed through the lumen, for this would cause local leakage. The wound and sutures are then dusted with penicillin and sulphadimidine ('Sulphamezathine') powder (I.C.I.) and covered with a light dry gauze dressing secured with adhesive tape.

Between dressing and glass connection projects a sufficient length of tubing for squeezing or milking to free either end of the system from clots and fibrin; a gurgling inside the wound proves the collecting end to be patent. This is done two or three times daily in the ward. Union between the drain and the thin-walled rubber tubing is made over an angled or straight flanged Paul's tube, and must be rendered watertight by secure binding with thread, for a leak at this junction soils the bed-clothes. The thin collapsible tubing is led to a glass jar suspended from the bed; it is light and prevents drag on the wound, and even when obstructed from time to time

RESULTS

Surprisingly large volumes are collected from big wounds as much as 10 oz. m for the first four or five days. A radic wound (fig. 2) will yield on an average serum in twelve days. With open drai would have to be collected into expe frequently changed, whereas with sealed have found it seldom necessary to disturb the theatre wound coverings.

The enthusiastic appreciation of the nurses is testimony of the value of this method.

In this way the management of all our radical mad tomy cases has become a simple matter, and in last two years there has been no instance of gross wo sepsis, sloughing, or tenting from large subcutane gatherings of serum.

The routine postoperative use of penicillin for ten fourteen days has, of course, been partly responsible these good results.

Mr. Hedley Atkins also originated the idea of managi his mastectomy wounds in this most successful manne

The pleural cavity after any form of combined gast œsophageal resection drains happily with the ribb tube (fig. 1B), the soft collapsible rubber tubing acti as a good valve and obviating the need of a water It is stated that any thoracotomy tube should be rem after forty-eight hours when drainage ceases, bu tubes have continued to work well up to fourteen while awaiting sound healing of the anaston Empyemata, after all, have been dealt with in this since Tudor-Edwards designed his ingenious tub years ago. It was in fact his example which me to use a sealed drain with collapsible tub both as an air valve and conveyor of the pus.

The firm closure, with buried 'Nylon' sutur intercostal wound round the neck of the collec gave such a clean and lasting seal that th seemed worth a trial in many other situations.

Admittedly it is rarely that one has to drai so large as the pleural cavity, but an efficient c tube correctly placed in the main reservoir of an will continue to gather fluid from neighbouring and layers until its work is done.

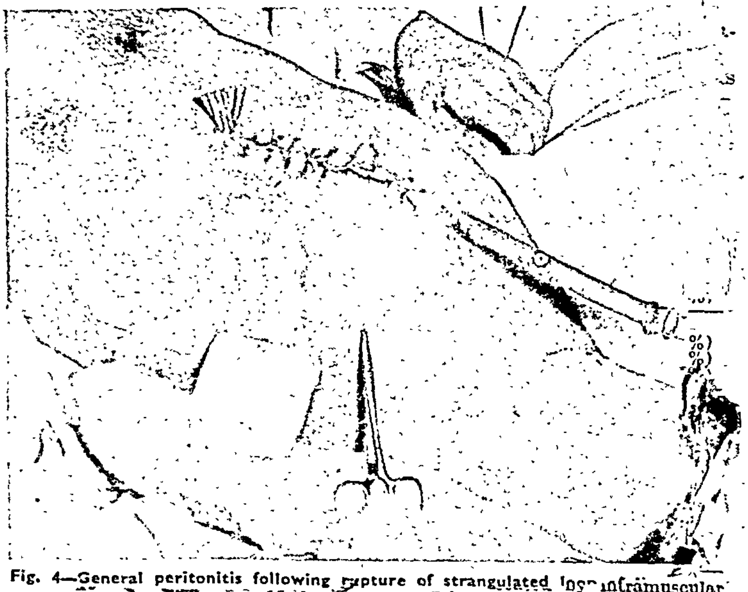

Fig. 4—General peritonitis following rupture of strangulated [illegible] intramuscular [illegible] with a 13 [illegible] corrugated [illegible] and are included in this

[illegible] who survived it was necessary to stop for a time.

It is sugg
an imbalance nage following cholecystectomy and chole-
depressor mecl 3) has proved a real blessing. Any escape
adrenal gland e early clamping of the T-tube is carried
therapy shoul bottle, and the wound is spared many
tensive patien e patient is without the usual mess and
inhibits the p a sore skin, for even after extraction of
adrenal corte wound drain is retained until all leakage
decreasing th
thectomy operation wounds can be treated in the same
inhibi and there need be no hesitation in dealing with
ower abdominal collections of fluid in like fashion
4). The right iliac fossa, after removal of a ruptured
Davi ndix, clears itself quite as well through the sealed
n as along the usual piece of corrugated rubber.

As a safety measure following partial colectomy the
bed tube can be left down to the site of the anasto-
sis until all danger of leakage and delayed suppuration
s passed, and thus an occasional tragedy can be
G erted.

Any prostatectomy wound, even with secure bladder
G
L osure, requires drainage of the prevesical space, from
hich a surprisingly large quantity of fluid usually
capes. This is effectively collected by a small type-A
ibe with its end split and each half tucked snugly
ito the space on either side of the bladder wound.
dry dressing and the prevention of leakage on to the
tient's groins and scrotum make for postoperative
fort and healthy wounds.

ie practice of dusting our potentially infected wounds
Cally with penicillin and sulphadimidine powder
for urag s the formation of much watery fluid which
dicitates the initial flow into the collecting-tube and
to prevent clotting and obstruction.
the out ursing of a patient after an abdominoperineal
the body is reduced to a simple task, for the type-C
avoidan d tube may be left in the pelvis for two or
sound eks with the perineal wound dry and healthy
infectio sure areas amply safeguarded (fig. 5). In all
to com ly closure of the sinus has attended the removal
convale be, and none of our perineal wounds has broken
The

(1) ound healing achieved with buried nylon sutures
tion, w the most septic wounds has justified the universal
atmos of every incision with monofilament nylon single
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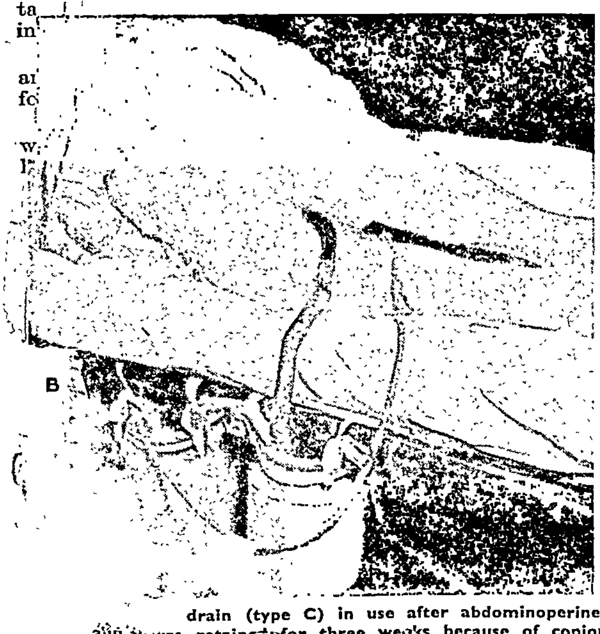

drain (type C) in use after abdominoperineal
and ... retained for three weeks because of copious
; C, corrugated type ... healthy and s ... urine into closed a ... separate receptacle.

strands with the minimum of deeply buried knots. Thus watertight closure around the drains is maintained, whereas the early disintegration of catgut often led to leakage and much reaction in the surrounding tissues. Our nylon-sutured wounds, in spite of initial heavy infection, have healed well, and the proportion requiring subsequent removal of the buried sutures is remarkably small.

Scar hernias have not yet been seen, but it is perhaps a little early to be too certain about the benefits of closed drainage and nylon in this respect. Part of the credit here must go to the routine use of antibiotics, for the prevention of secondary infection and wound contamination is the prime factor in ensuring sound healing.

CONCLUSION

Sealed drainage has been used for the past two years in all wounds needing it; at no time has this system had to be abandoned because of pocketing or blocking of our special tubes.

The comfort of the patient, the cleanliness of his garments and bed-clothes, and the healthy appearance of his wound have all been convincing evidence that efficient drainage can be safely secured with the methods described.

Much saving has been achieved in the use of dressings (the price of which continues to soar), and also in time and labour.

THE RESULTS OF TREATMENT OF TUBERCULOUS MENINGITIS WITH STREPTOMYCIN

FRANK ROBERTSON
M.D. Durh., M.R.C.P.
PHYSICIAN, GENERAL HOSPITAL, BISHOP AUCKLAND;
SOMETIME FIRST ASSISTANT, DEPARTMENT OF MEDICINE,
KING'S COLLEGE, NEWCASTLE UPON TYNE

DOUGLAS GAIRDNER
D.M. Oxfd, F.R.C.P.
PÆDIATRICIAN, ADDENBROOKE'S HOSPITAL, CAMBRIDGE;
SOMETIME FIRST ASSISTANT, DEPARTMENT OF CHILD HEALTH,
KING'S COLLEGE, NEWCASTLE UPON TYNE

THIS paper gives the results of treatment with streptomycin in 146 cases of tuberculous meningitis. The study was established in the children's department of the Royal Victoria Infirmary, Newcastle upon Tyne, and extended to other departments and hospitals; but the responsibility for diagnosis, observation, and clinical records remained in our own hands, and all the patients were supervised during the treatment and followed up afterwards by one or both of us. This method of personal responsibility, and the length of the period of observation —24–51 months (on Dec. 1, 1951)—will be a measure of the validity of our conclusions. Since streptomycin was the main or only form of treatment which we used, this record of our study may serve as a yardstick against which the therapeutic effects of adjuvants to streptomycin can be measured.

MATERIAL

146 patients were treated in five hospitals in Newcastle upon Tyne in collaboration with the medical staffs of these hospitals. The first patient was admitted on Aug. 30, 1947, and the last on Nov. 30, 1949. Between May, 1948, and September, 1948, children aged less than 3 years and advanced cases were not accepted for treatment. After September, 1948, there was no selection, and treatment was given to all cases.

Broadly the cases fall into two main groups. The f group, of 27 cases, consists chiefly of the earliest sp and these were treated either with intramuscular and intrathecal therapy, with regular rest periods in the intrathecal therapy. The second group, of 119 cases, was treated by combined intrathecal and intramuscular therapy without planned rest periods. The two groups cannot be compared, but both are included because we believe that information is needed chiefly on two main points: (1) the long-term results of treated tuberculous meningitis, and (2) the results of therapy using a single scheme of treatment. The first group contains those with the longest period of survival and is useful for the first aim, and the second group yields information of use for both aims.

CRITERIA OF DIAGNOSIS

Since it was unusual to find tubercle bacilli in the first specimen of cerebrospinal fluid (C.S.F.) examined, treatment was generally started on a finding of a characteristic C.S.F. (pleocytosis and diminished sugar content) in a patient whose history and clinical signs indicated to experienced clinicians that the disease was tuberculous meningitis, together with evidence of tuberculosis elsewhere and a positive Mantoux test. In most cases final bacteriological proof was obtained either by the demonstration of tubercle bacilli in the C.S.F. by culture or guineapig inoculation or at necropsy. There were 7 cases in which the patients survived and bacteriological proof was lacking, but all these ran a clinical course typical of tuberculous meningitis, and we have not hesitated to include this small group.

DEFINITION OF SEVERITY

Criteria for the definition of the severity of the disease were those recommended by the Medical Research Council (1948). The same groups—miliary and meningitis on admission, miliary developing meningitis under streptomycin treatment, and meningitis without miliary—were used.

DOSAGE SCHEDULE

Intramuscular therapy was the same in all cases: 2 g. daily was given to adults; 1 g. to children aged 5–14 years; and 0·5 g. to children aged less than 5 years. The dose was divided and given twice daily.

Intrathecal therapy was given in doses of 0·1, 0·05, and 0·025 g. in the above-mentioned age-groups respectively.

In the first group daily intrathecal therapy was usually given for six weeks followed by one or two weeks' rest. It was a deliberate policy to provide rest periods, but in this early group of cases there was a good deal of variation in treatment, and nothing is to be gained by analysing the technique closely.

In the second group, of 119 cases, intrathecal therapy followed a general pattern with only small individual variations. *Daily* injections were given for 7 days. A clinical assessment was then made, C.S.F. findings being ignored at this stage. If the patient had clearly improved, had less headache, was mentally lucid and coöperative, and had less neck stiffness, the dosage was reduced to *alternate days*. If such improvement was not evident, daily intrathecal therapy was continued a further seven days and, if necessary, for another seven days. In the great majority of cases by the end of twenty-one days either some improvement had taken place or decerebrate rigidity had developed. In a few the condition was doubtful, either stationary or fluctuating; these, too, were stopped at twenty-one days, and thereafter treatment was continued on alternate days.

Rest Periods

The *intramuscular* treatment was stopped only if abscesses or severe pain or much loss of morale developed. Therapy was stopped then for seven days. About half the patients had a rest of seven to fourteen days somewhere during treatment.

The *intrathecal* treatment was similarly only stopped if much loss of morale developed, and in 30 patients out of 60 who survived it was necessary to stop for a time. The supervention of complete spinal block of course prevented therapy via the lumbar route, in which case the cisternal or ventricular route was generally used.

Determination of End-point of Therapy

In the second group, of 119 cases, we originally intended to continue treatment until a state of clinical well-being was reached, with a normal C.S.F.—cells less than 5 per c.mm., protein 40 mg. or less per 100 ml., sugar 50 mg. or more per 100 ml.—but in about a third of the cases treatment was stopped before complete normality was reached. This was because, as experience accrued, we found that, when treatment was stopped, in some cases the C.S.F. gradually became normal later. Though 2 patients recovered after three months' treatment, and 3 needed more than fifteen months', most of them required 5–11 months' treatment, there being almost the same number in each of these intervening months.

OTHER TREATMENT

This report is chiefly concerned with the results of streptomycin as the sole treatment. Other forms of treatment have been used in a few cases, but consideration of these will show that the small proportion so treated, and the late stage at which this additional treatment was begun, make their effect small in this series as a whole. Streptokinase was used in 3 cases; 1 patient survived. Para-aminosalicylic acid was given to 2 adults with phthisis; 1 survived. Purified protein derivative, sulphetrone, and heparin were not used.

Surgery was used mainly in the late stages and as a last resort.

22 patients had some form of surgery, including a woman admitted originally with presumed subdural hæmatoma, in whom a ventriculogram revealed hydrocephalus and the C.S.F. contained tubercle bacilli; treatment was continued via a needle through the burr holes, and she recovered.

In 2 cases a tuberculoma had been removed two months and three weeks before the onset of meningitis; streptomycin was injected into the subarachnoid space through the wound; both patients died.

In 11 cases a last-minute attempt was made to treat severe hydrocephalus with decerebrate rigidity; all the patients died.

4 cases had ventriculograms because of continuing papillœdema, and 1 of these showed no evidence radiologically, or in respect of C.S.F. pressure, of hydrocephalus; all the patients recovered.

4 patients were operated on because they were not doing well and a block was suspected; 1 died.

TABLE I—RESULTS OF TREATMENT IN 146 CASES OF TUBERCULOUS MENINGITIS *

ANALYSED IN TERMS OF ADMISSION STATE, AGE, AND DIAGNOSIS

—	Series I (27 cases)		Series II (119 cases)	
	Total	Recovered	Total	Recovered
Admission state:				
Early	9	7 (*78%*)	33	21 (*64%*)
Intermediate	15	2 (*13%*)	54	34 (*63%*)
Late	3	0	32	5 (*16%*)
Total	27	9 (*33%*)	119	60 (*50%*)
Age (yr.):				
Less than 3	9	3 (*33%*)	35	11 (*31%*)
3–14	8	3 (*38%*)	52	32 (*61%*)
More than 14	10	3 (*30%*)	32	17 (*53%*)
Total	27	9 (*33%*)	119	60 (*50%*)
Diagnosis:				
Meningitis without miliary	17	7 (*41%*)	72	42 (*58%*)
Miliary and meningitis on admission	5	1 (*20%*)	39	16 (*41%*)
Miliary developing meningitis under treatment	5	1 (*20%*)	8	2 (*25%*)
Total	27	9 (*33%*)	119	60 (*50%*)

* Of 33 cases of miliary tuberculosis treated by intramuscular injections, 13 developed meningitis and are included in this report.

TABLE II—C.S.F. STATE OF 69 SURVIVORS

State on admission	Series I (27 cases, 9 survivors)		Series II (119 cases, 60 survivors)	
	Normal C.S.F.	Abnormal C.S.F.	Normal C.S.F.	Abnormal C.S.F.
Early	6	1	15	5
Intermediate ..	2	..	23	11
Late	..	..	2	4
Total ..	8	1	40	20

In series I and II combined, of 69 survivors 48 (70%) have normal C.S.F.

RESULTS

The patients who completed their treatment have been followed up at regular intervals. On Dec. 1, 1951—i.e., at least twenty-four months after treatment was begun—77 patients had died, leaving 69 survivors, all of whom were known to be free from clinical symptoms of active meningitis. Most of them were at home, unless some extrameningeal tuberculous lesion was requiring treatment. The state of affairs on Dec. 1, 1951, is given in three tables. Table I gives the numbers surviving according to admission state, age, and form of disease; table II gives the proportion of these survivors achieving normal C.S.F.; and table III gives a summary of the clinical state of the survivors.

RECRUDESCENCE

Recrudescence occurred in 11 patients out of 22 clinically well but still having an abnormal C.S.F. 7 of these died after a further course of treatment. 4 recovered and are still well and, of these, 3 now have a normal C.S.F. There are now 48 patients with normal C.S.F. Information on the latest C.S.F. findings in the remaining 11 cases with abnormal C.S.F. is lacking, and some may now be normal. There were 49 cases with normal C.S.F., and of these 1 has relapsed:

Case 1.—A girl, aged 2 years on admission on Sept. 20, 1948, developed meningitis while in hospital with a primary lung lesion. She was treated for twenty-one days with continuous intrathecal therapy and thereafter on alternate days for three months, intramuscular therapy being given throughout. When treatment ceased, the C.S.F. was steadily returning to normal (protein had decreased steadily from 180 to 65 mg. per 100 ml., and cells from 240 to 40 per c.mm.). The child was clinically well but ataxic. On Aug. 8, 1949, the C.S.F. contained no cells, protein 35 mg. per 100 ml., and a normal amount of sugar. Thereafter the C.S.F. was examined periodically and remained normal for the next four months, the last C.S.F. examination being in January, 1950. A month after this examination the child had a fit, and a second fit occurred in March, 1950 (her mother was epileptic); otherwise she remained well. She developed nocturnal enuresis in February, 1951, and was thirsty. There were no abnormalities on examination, and the urine was normal and sterile. A brother had just returned home after an operation for tuberculous kidneys. It was decided to admit her for renal investigation, but before this was done she was readmitted on April 9, 1951, with meningitis; she was clear mentally but had a three days' history of headache and vomiting. The C.S.F. contained protein 120 mg. per 100 ml., and 437 cells per c.mm. Treatment was started again and was completed in August, 1951; she remains well, but the C.S.F. is still abnormal.

TABLE III—CLINICAL STATE OF THE 69 SURVIVORS

[illegible]al C.S.F. (48 patients):
[illegible]e deaf—1 partially, 2 completely.
[illegible]ve developed tuberculous knee-joints, a 3rd tuberculous hip, [illegible]d a 4th a tuberculous ankle.
developed a tuberculous abscess of the chest wall, which has recovered.
1 has ocular palsies, which give no trouble.
1, aged 4 months at onset of meningitis and now aged 4 years, *is probably mentally retarded.*
1 relapsed, had further treatment, is now well, but still has an abnormal C.S.F.

Abnormal C.S.F. (21 patients):
1 has had two blackouts and one attack of loss of memory in a year.
1 has a left hemiplegia and is slowly improving.
1 has developed uncinate fits twenty-six months after the end of treatment (? due to cerebral tuberculoma). These have now apparently ceased.
1, aged 4 years, is completely deaf and is losing the ability to talk.
1 has left homonymous hemianopia, which apparently causes no trouble.
1 late case on first admission relapsed and has done well on further treatment, which only ceased on Dec. 1, 1951. C.S.F. is still abnormal.

Total (69 survivors):
4 have developed osseous lesions.
4 are deaf.
1 is probably mentally retarded.
6 have miscellaneous lesions.
The remainder are well, but all show varying degrees of ataxia in the dark, which causes no real bother.

PROGNOSIS

From an analysis of this series it is impossible t define the influence on prognosis of any of the followin factors: age, existing miliary tuberculosis, length c history, development of meningitis during treatmen of miliary tuberculosis with streptomycin, choroida tubercles, and papillœdema. The only guide on admissio is the clinical picture based on a combination of psycho logical and physical findings. Under treatment thre main patterns seem to emerge:

(1) *Rapidly Successful*

A few, usually early, cases show considerable clinica improvement within seven days of starting treatment and by fourteen to twenty-one days the patients ar sitting up, mentally alert and happy, coöperating wel in their treatment, afebrile, and without neurologica change, except perhaps diplopia. These patients neve cause any anxiety, are soon out of bed, and seem t recover fully. One gets the impression that they ar going to recover after four to eight weeks and that long treatment may not be necessary. There were 7 such cases in this series.

(2) *Decerebrate Rigidity*

At the other extreme is the patient who is admitted with decerebrate rigidity or who develops it soon after the start of treatment. No such patient in this series or seen subsequently by us has recovered from this state. Indeed we have wondered if the attempt to obtain recovery was justifiable, because it seems that there might be a high risk of severe mental and physical changes. A composite picture of this state may be described as follows:

The appearance is one of tonic rigidity, chiefly in extension; the head and neck are thrown back, and opisthotonos is usually present with the legs extended and the feet plantar-flexed. The upper limbs are extended, with the hands flexed at the wrists, the fingers curved into the palms, and the forearms excessively pronated. Attempts to flex the limbs and spine meet with great resistance. The head is rotated sideways, and the eyes may deviate to that side. The picture resembles that of torsion spasm arrested in the middle of a movement. Chewing movements of lips and jaws and constant sucking movements or teeth grinding may be observed. At times an unusual type of "fit" may come on; the limbs seem to become even straighter, the arms swing round behind the back, the head and neck are thrown farther back, and the spine is more arched. This is the "tonic spasm" or "cerebellar fit." Any attempt to handle the patient at first provokes no response. Then, after a few seconds, a grimace slowly appears and spreads over the face, and a loud piercing wail is emitted. The wail and grimace die away very slowly after the stimulus is withdrawn. Later the grimace and wail appear without any obvious external stimuli. At times various colour and sweating changes take place. For an hour or two the face may be flushed scarlet and the limbs pale. Beads of sweat may cover the forehead. Later the face becomes pale, and the limbs may be hot and red. Death is often presaged by an abrupt rise in temperature to 104°F or more.

In this series 47 patients showed decerebrate rigidity in its fully developed form, and none recovered.

(3) *Cases with Fluctuating Course*

Unfortunately these comprise the majority, whether early, intermediate, or late cases. The condition of the patient fluctuates for several months both as regards clinical state and C.S.F. findings, and improvement rarely takes place in less than four months. Severe mental disturbances may occur. 3 patients were stuporose for three months, but all recovered fully. One girl could only say "I want my breakfast"; she continued saying this almost all the time she was awake for six weeks, and steadily grew thinner, despite a large appetite; but she finally recovered, and has passed her scholarship examination for entrance to a secondary school. Delirium and confusion may persist week after week for three or four months; squints, hemiplegia, headache, neck stiffness, vomiting, papillœdema, loss of weight, poor appetite, and fever may all wax and wane for up to six months. The C.S.F.-protein level may fluctuate and rise to 600 mg. or more per 100 ml.; blocks may develop, and hence surgery may be attempted.

As month succeeds month one is overcome by a sense of helplessness. Yet after six or nine months some such patients begin to improve slowly, whereas others deteriorate and die. At present we have not been able to say what determined the change, or to indicate any prognostic features. However, no matter how ill the patient becomes, mentally or physically, or what the changes in the C.S.F. are, so long as the picture of decerebrate rigidity does not develop there is always hope of recovery even after a year. Therefore treatment must not be given up in these cases, however discouraging at the time it seems to be.

It is in this group that one feels the need of adjuvants to streptomycin. Yet it is just in this group that it will be hard to assess the value of such adjuvants without more knowledge of the patterns of behaviour of tuberculous meningitis modified by streptomycin. There is a large field here for accurate clinical observation and recording.

Case 2.—A boy, aged 18, took ill with cough and hæmoptysis in December, 1947. On May 3, 1948, he developed meningitis, and on May 22, 1948, he was admitted to hospital with headache and vomiting. He was rational but inattentive and had neck stiffness and a left external rectus paralysis. His C.S.F. contained 755 cells per c.mm. (70% lymphocytes), protein 250 mg. per 100 ml., no sugar, and chlorides 590 mg. per 100 ml. Tubercle bacilli were obtained on animal inoculation and culture of the C.S.F. Radiography of the chest showed a primary complex and miliary tuberculosis.

Treatment was started on May 22, 1948, intrathecal therapy being given daily for seven days and then on alternate days. At the end of the first week the patient was drowsy, but the headache and neck stiffness had gone. Three weeks after admission he developed a right hemiplegia, and in the fourth week papillœdema appeared. His right pupil was then dilated and reacted very sluggishly, to light and on convergence. He was more drowsy, and the C.S.F.-protein level had risen to 600 mg. per 100 ml. From the fifth to the ninth week he could be roused only with difficulty and lay all day silent and still. He had extensor plantar responses, much neck stiffness, a coarse tremor of the hands when he moved them, nystagmus, and incontinence of urine and fæces; caloric tests showed hypofunction of the labyrinth. During these weeks the hemiplegia slowly improved; and the C.S.F.-protein level fell from 600 to 280 mg. per 100 ml. and the cells fluctuated from 600 to 300 per c.mm. of C.S.F.

Since the patient struggled when lumbar puncture was attempted, and it became very difficult to continue, seven days' rest from intrathecal therapy was given at the end of the ninth week. His condition fluctuated thereafter. He sometimes spoke a little, but his memory was bad. He could not recall his work as a miner, and sometimes said he had not had anything to eat, but he ate ravenously all the time he was fed. In the eleventh week the papillœdema disappeared, and at the end of the fourteenth week intrathecal therapy again had to be stopped because of his struggles. The C.S.F. then contained protein 320 mg. per 100 ml. and 200 cells per c.mm. Radiography in the sixteenth week showed clearance of the miliary shadows. By the eighteenth week the tremor had gone, and the patient was beginning to move slowly and infrequently about the bed and even to feed himself when urged. Mentally he remained disoriented, had no memory—e.g., he did not remember eating his last meal or receiving his last intramuscular injection. He gradually improved and got up, and his mother asked to take him home in the twentieth week for two weeks. Treatment was then stopped. At home he did not recognise anyone and could not carry on a conversation. On return to hospital his movements were quicker, and he talked a little more and smiled more readily, but he could not remember being in hospital previously. His C.S.F. was unchanged. In view of the previous difficulties in giving treatment we decided reluctantly against further treatment and observed him. He steadily improved, the nystagmus ceased, and the plantar responses became flexor again. Sight and hearing were normal. He remained ataxic. The C.S.F. slowly improved; the protein level fell to 120 mg. per 100 ml. and cells to 52 per c.mm. in the twenty-fourth week. He gradually grew extremely fat and was very fatuous and childish. He returned home and did better this time, taking a little interest in life.

Follow-up.—He very slowly continued to improve, and on March 23, 1950, had begun to lose some of his superfluous fat and talked quickly and rationally; there were no abnormalities on examination of the nervous system, except much ataxia in the dark. In the past six months he had had three attacks of loss of memory, each preceded by a bout of vomiting. The C.S.F. when last examined on Jan. 10, 1949, contained protein 140 mg. per 100 ml., cells 15 per c.mm., and sugar normal. Radiography of the chest was normal on Aug. 19, 1951. He was then brisk and cheerful, and engaged to be married; and, apart from ataxia when walking with his eyes shut, there were no abnormalities on examination. He had had one more attack of amnesia lasting a day in January, 1951, which came on after visiting a cinema. No evidence suggesting a fit was obtained.

PREGNANCY

6 of our cases have been associated with or followed by pregnancy.

Case 3.—A woman, aged 25, was admitted with tuberculous meningitis of intermediate severity on Oct. 4, 1947. She had missed a period before admission and was pregnant. She improved for a while on treatment, but then developed a spinal block, and intramuscular treatment only was continued. She came into labour at the expected time and was delivered by cæsarean section of a healthy baby. She died of the meningitis two days after delivery. The baby was well and thrived until it was 6 weeks old, since when we have lost touch with it.

Case 4.—A girl, aged 19, fell down when seven months pregnant and was admitted on April 24, 1949, as a case of head injury and then found to have tuberculous meningitis of intermediate severity. While on treatment she developed a left hemiplegia and also became ataxic. The baby was delivered normally at full term while the mother was still on treatment, and is thriving. The patient's hemiplegia is clearing, and she is looking after her husband and the baby.

Case 5.—A woman, aged 24, recovered from meningitis on May 7, 1948, and was perfectly well apart from ataxia, and lived a normal life. She has subsequently married and was delivered of a healthy child in April, 1951.

Case 6.—A girl, aged 19, recovered from miliary tuberculosis and meningitis on May 28, 1948, but was deaf and ataxic. She has married and runs her own house and was delivered of a normal baby in May, 1951.

Case 7.—A woman, aged 24, recovered from meningitis on Jan. 31, 1949, but was ataxic and had pulmonary tuberculosis. She became pregnant and was delivered of a healthy child in October, 1950, and both are now well.

Case 8.—A woman, aged 22, developed meningitis on Jan. 19, 1949. She went into labour at home and delivered herself of a full-term healthy baby on Jan. 25, 1949. Thereafter she deteriorated and was admitted to hospital on Jan. 27, 1949, with advanced tuberculous meningitis. She rapidly developed decerebrate rigidity and died on Feb. 27, 1949. The baby has remained well.

COMMENTS

Our present scheme of treatment follows the scheme adopted for series II with daily intrathecal therapy for one to three weeks, depending on the clinical condition, followed by injections on alternate days. Intramuscular and intrathecal therapy is continued until the clinical condition is clearly improving, the patient is mentally alert and ambulatory, and the C.S.F. is showing steady signs of improvement. Usually this requires three to six months. Intrathecal therapy is then stopped, but intramuscular therapy is continued. Lumbar puncture is done weekly. If the C.S.F. deteriorates, the lumbar puncture is repeated; and, if this deterioration is confirmed, intrathecal treatment is begun again on alternate days. If, however, the C.S.F. remains unchanged and the clinical condition is good, further intrathecal therapy is withheld. When it is clear that without intrathecal therapy the C.S.F. is still returning to normal, the weekly lumbar puncture is discontinued. At this stage, provided there is no radiological evidence of miliary tuberculosis and no other reason, such as pulmonary tuberculosis or bone tubercle, which merits intramuscular streptomycin, then intramuscular therapy is also stopped, and the patient goes home. He returns in a month for further lumbar puncture, and continues to do so until the C.S.F. is normal. If at any time headache or vomiting occurs, he reports back to hospital immediately.

Until C.S.F. normality has been achieved, the outlook *remains uncertain, and relapse is an ever-present danger.* Only 1 case in this series has relapsed after attaining a normal C.S.F., although another such case has been seen.

Although occasional patients may recover on intramuscular streptomycin alone (one of our earliest patients remains well after four years), there is universal agreement that intensive intrathecal treatment is essential, but there is considerable difference of opinion on two points: the amount of streptomycin to be given in any one intrathecal dose, and the frequency of injections.

Amount of streptomycin to be given in a single dose.—The dosage we used (adults 0·1 g., children aged 5–14 0·05 g., children aged less than 5 years 0·025 g.) is generally used in this country, but in America and in some Continental centres the tendency has been to use smaller doses. The purer preparations of streptomycin produced today cause little irritation when introduced into the subarachnoid space, and the only toxic effect of significance is upon the 8th nerve. Loss of *vestibular* function probably takes place in all the patients who receive frequent intrathecal injections of streptomycin, even if the dosage is much smaller than the scale above. None of our patients is known to have recovered this function once it has been lost, yet the only disability noticeable is when moving in the dark. *Deafness* remains therefore the only important toxic effect. This was present in 4 of 67 survivors (6%), but it is impossible to know whether streptomycin or meningitis was the main factor in these. This relatively low incidence of deafness suggests that the dosage is not too high. (The great majority of patients received only streptomycin; only a few received dihydrostreptomycin.)

Frequency [illegible] *thecal injections.*—The recent tendency in [illegible] es has been to give daily intrathecal injectio[illegible] any weeks, whereas we have *continued with a* [illegible] urse *of daily injections* followed by a long course o[illegible] lternate-day injections. Formal comparison of our results with those of other centres is impracticable. For such a comparison to be of value the degree of selection of cases must be stated, the state of the patients before treatment comparable, the follow-up long, and the clinical and C.S.F. findings in the survivors described. Further, the number of cases must be very large, or the effect of even important advantages in treatment may not be apparent. This is because in any series there will be cases, such as those already described above, which seem to do well under almost any system; there will also be cases in which irreversible neurological changes, best shown by encephalography (Lorber 1950), are already present at the start and make cure hopeless. Differences in the effectiveness of different treatments of the remaining cases therefore tend to be diluted or obscured.

In series II, of 119 patients 58 (50%) recovered; and of these at least 69% achieved normal C.S.F. If late cases are excluded, there are 87 patients of which 55 (63%) recovered, at least 40 of these (73%) having normal C.S.F. These results compare favourably with those of other series, such as those listed by Cathie and MacFarlane (1950) and Illingworth and Lorber (1951), and we conclude that the scheme we have used is at least as effective as any other available for comparison.

SUMMARY

The results of treatment of 146 patients who developed tuberculous meningitis between August, 1947, and November, 1949, are described.

Treatment was by streptomycin alone in 141 of the 146 patients and followed a uniform schedule in most cases.

There are 69 survivors, most of whom are free from meningitic symptoms or sequelæ, apart from ataxia in the dark; 48 have a normal C.S.F.; 4 have subsequently developed tuberculous osseous lesions.

The results of pregnancy during or after tuberculous meningitis are cited in 6 cases.

The fluctuating course taken by many cases under treatment is emphasised; recovery may eventually come after many months of continued severe physical and mental illness. Decerebrate *rigidity*, however, has in our experience proved invariably fatal.

A suggested scheme for streptomycin treatment is given.

Obviously so large a series treated in five hospitals has called for an unusual degree of coöperation from many people, whose assistance so freely given it is a pleasure to record. Successive house-physicians and registrars gave *invaluable* help. Especial thanks are due to Dr. George Brewis and Dr. C. Neubauer, at Walkergate Hospital, Dr. George Davison, at Newcastle General Hospital, and Dr. C. A. Green, of the department of bacteriology at the Royal Victoria Infirmary. The physicians, radiologists, and pathologists at the hospitals mentioned and at the Fleming Memorial Hospital for Sick Children helped with various cases, and Mr. G. F. Rowbotham and Mr. J. Whally gave the surgical treatment. Prof. Sir James Spence and Prof. F. J. Nattrass exercised a general *supervision and gave constant encouragement.*

REFERENCES

Cathie, I. A. B., MacFarlane, J. C. W. (1950) *Lancet*, ii, 784.
Illingworth, R. S., Lorber, J. (1951) *Ibid*, ii, 511.
Lorber, J. (1950) *Arch. Dis. Childh.* 25, 404.
Medical Research Council (1948) *Lancet*, i, 582.

HALLUX VALGUS

PREDISPOSING ANATOMICAL CAUSES

R. H. Hardy
M.A., D.M. Oxfd
SATRA RESEARCH FELLOW

J. C. R. Clapham
B.A. Camb.
SATRA STATISTICIAN

DEPARTMENT OF ANATOMY, UNIVERSITY COLLEGE, LONDON

Hallux valgus and the *bunion it causes* are responsible for much disability and suffering, especially among women about the age of 50. At the Royal National Orthopædic Hospital in May, 1949, the waiting-list for Keller's operation contained the names of 250 people, most of whom had a painful bunion (Hardy and Clapham 1951). Treatment of this condition in its advanced stages takes a long time and is not always satisfactory.

Almost nothing is known of the ætiology of hallux valgus. It is supposed to be associated with metatarsus primus varus, and this has been borne out by measurements on Canadian troops (Harris and Beath 1947). A high correlation has been shown between the degree of displacement of the great toe and the size of the angle between the first two metatarsals (Hardy and Clapham 1951). But examination of adults has not provided conclusive evidence that either a wide intermetatarsal angle or advancing age are responsible factors.

We therefore decided to examine children's feet for possible evidence of an anatomical predisposition to

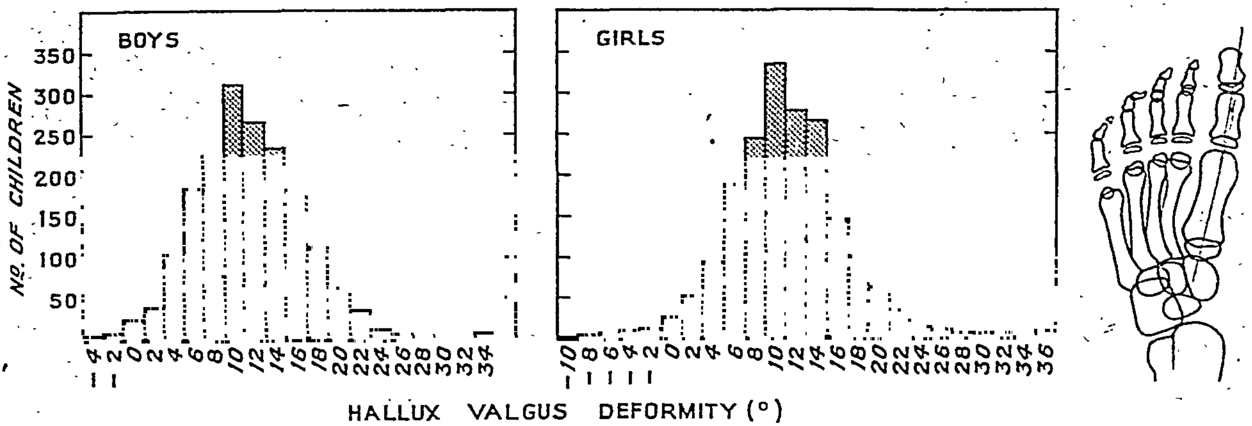

Fig. 1—Distribution of hallux valgus deformity, measured as degrees of displacement of proximal phalanx from metatarsal axis.

hallux valgus. If, for instance, some children have an abnormally large intermetatarsal angle, which does not increase materially with age, and show increasing hallux valgus as their age advances, it would be clear that this angle could be a factor in the causation of the deformity.

METHOD

Using a standard radiographic method, we examined school-children from a residential area in Middlesex lying between Harrow, Greenford, and Ruislip.

This region is a modern housing district some of whose inhabitants go daily to central London and others to the many light industrial factories in the district. Of the children examined, the infants (aged 4), juniors (5–10), and senior girls (11–15) were all taught in a single conglomeration of buildings in South Harrow; the senior boys were taught at Greenford, about two miles away.

In all, 1851 children were examined, but there was an inevitable small wastage of results from various causes. The distribution of sexes was approximately equal, and except for the extreme ages (4 and 15) there was a more or less consistent annual age-distribution.

The reliability of measurements on standard radiographs of the foot has been assessed by Venning and Hardy (1951). In the present inquiry an exposure of both feet was made on a single film to save time and material; the X-ray tube was placed vertically above a point mid-way between the first metatarsal heads at a target-film distance of 100 cm. By this method angular measurements can be made with an expected accuracy of ±0·5° (standard deviation).

RESULTS

For simplicity the findings are given in figures representing numbers of feet and not of children.

Position of Hallux

In 3642 feet the mean position of the hallux (measured as the angle between the axes of the proximal phalanx and the first metatarsal) shows a lateral deflection of 12·0° ± 5·1°. The distributions for boys' and girls' feet are given separately in fig. 1. There is no significant difference between the distributions for each sex.*

TABLE I—DISTRIBUTION OF VALGUS DEFORMITY AMONG AGE-GROUPS

Age (years)	No. of feet		Mean angle and standard deviation (degrees)		
	Boys	Girls	Total	Boys	Girls
4–5	238	214	10·0 ± 4·35	10·3 ± 4·22	9·6 ± 4·47
6–7	338	354	9·6 ± 4·83	9·9 ± 4·63	9·4 ± 5·01
8–9	264	275	11·7 ± 4·45	11·9 ± 4·62	11·4 ± 4·28
10–11	373	343	12·6 ± 5·21	12·5 ± 5·38	12·7 ± 5·02
12–13	402	462	13·6 ± 4·98	13·6 ± 4·83	13·7 ± 5·11
14–15	200	176	14·4 ± 4·93	14·8 ± 5·03	13·9 ± 4·79

Coefficient of regression on age, and standard error:
Total .. .. 0·54° ± 0·027° per year of age
Boys .. .. 0·50° ± 0·037° „ „ „ „
Girls .. .. 0·57° ± 0·038° „ „ „ „

If these findings are broken down into age-groups it is observed that there is a progressive increase of lateral displacement of the great toe with increasing age. There is no statistically significant difference between the coefficient of regression on age for the two sexes (table I).

First Intermetatarsal Angle

In 3642 feet the mean angle between the axes of the first two metatarsals was 7·4° ± 2·1°. The distributions for boys' and girls' feet are given separately in fig. 2. The means are 7·33° ± 2·04° in 1815 boys' feet, and 7·55° ± 2·06° in 1827 girls' feet; this sex-difference of 0·22° is statistically highly significant.

TABLE II—DISTRIBUTION OF INTERMETATARSAL ANGLE AMONG AGE-GROUPS

Age (years)	No. of feet		Mean angle and standard deviation (degrees)		
	Boys	Girls	Total	Boys	Girls
4–5	238	214	7·4 ± 2·18	7·8 ± 1·99	7·0 ± 2·31
6–7	338	354	7·2 ± 2·11	7·4 ± 2·12	7·0 ± 2·09
8–9	264	275	7·2 ± 2·03	7·1 ± 2·25	7·3 ± 1·80
10–11	373	343	7·4 ± 1·97	7·2 ± 1·95	7·7 ± 1·95
12–13	402	462	7·7 ± 2·02	7·3 ± 1·98	8·0 ± 1·99
14–15	200	176	7·6 ± 1·99	7·2 ± 1·87	8·0 ± 2·05

Coefficient of regression on age, with standard error:
Total .. .. 0·05° ± 0·011° per year of age
Boys .. .. −0·04° ± 0·016° „ „ „ „
Girls .. .. 0·14° ± 0·016° „ „ „ „

There is in this case no significant increase of intermetatarsal a BISHith advancing age in boys; there is, however, su B. Birm. increase in girls (table II).

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We were unable to measure displacement of the terminal phalanx upon the proximal, because the squat

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* The following terminology is used throughout:
"Not significant" means a probability of the finding being due to chance of more than 1 in 20 (> 0·05).
"Significant": probability less than 1 in 20 (< 0·05).
"Highly significant": probability less than 1 in 100 (< 0·01).
"Very highly significant": probability less than 1 in 1000 (< 0·001).

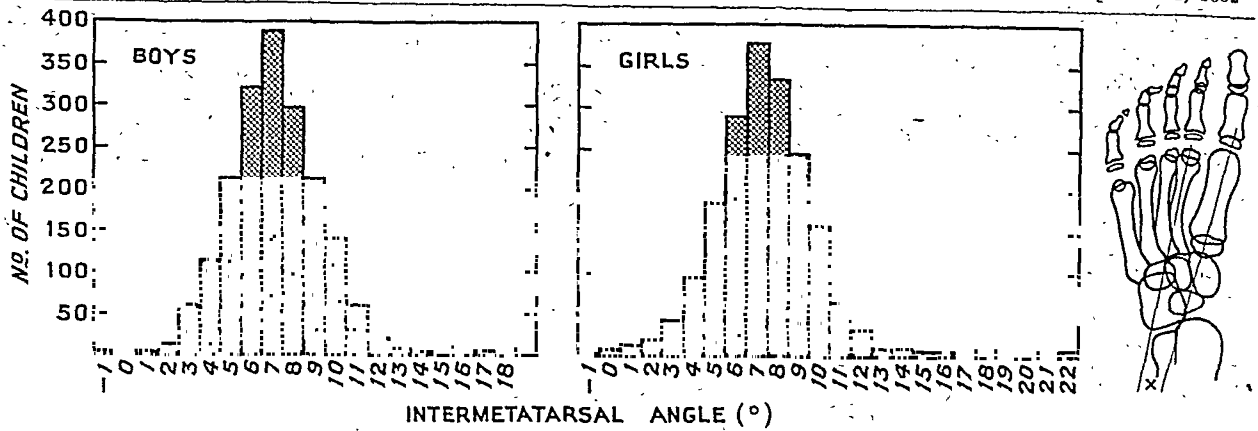

Fig. 2—Distribution of size of first intermetatarsal angle.

and irregular shape of the terminal phalanx made it impossible to determine its long axis either visually or geometrically. All we could do was to relate the two phalanges by an arbitrary scheme based on four degrees of displacement (fig. 3).

The mean displacement of the terminal phalanx upon the proximal in 3642 feet was 2·7 ± 0·5 units, and there was no statistically significant difference between boys and girls. With advancing age, however, the displacement of the terminal phalanx diminished (table III).

Analysis of Observations

In table IV the mean values of the three observations are compared in four groups—namely, children of 4–5 years, and of 14–15 years, adults suffering from symptomatic bunions, and a control group of adults. The similarity between the children and the adult controls suggests that they are members of the same statistical population, whereas the degree of hallux valgus and the size of the intermetatarsal angle in the morbid group are so clearly in a class by themselves, that they can probably be regarded as forming an abnormal group, not merely the outlying observations of a normally distributed population.

The figures for children and adult controls show that the increase in the displacement of the great toe occurs largely before the age of 14, and the increase in intermetatarsal angle occurs largely after the age of 15. The decrease in the deviation of the terminal phalanx takes place before the age of 15—i.e., during the time that the hallux valgus is increasing.

There are also individual children showing a degree of hallux valgus and an intermetatarsal angle well outside the expected adult range too highected range of variation may be laid down for any statistical observation in a given group by taking the mean ± twice the standard deviation of the group already studied. The odds against any individual being found with measurements beyond these limits are 20 to 1; or, to put it another way this range is that of the 0·05 probability level. The expected ranges thus obtained for displacement of the great toe and for the intermetatarsal angle are as follows: 4–28° for valgus in adults and 2–22° in children; 3–15° for intermetatarsal angle in adults and 3–12° in children. There are 11 children's feet with hallux valgus >28°, and 4 feet with intermetatarsal angle >15°. There is no statistically significant difference between the sexes. The extreme measurement for hallux valgus in children was 37° (in a girl of 12), and for the adult controls 36° (in a woman of 38). The greatest intermetatarsal angles were 22° (in a girl of 5) and 16° (in a woman of 25 and a girl of 19).

TABLE III—DISTRIBUTION OF TERMINAL PHALANX DISPLACEMENT AMONG AGE-GROUPS

Age (years)	No. of feet		Mean displacement and standard deviation (arbitrary degrees)		
	Boys	Girls	Total	Boys	Girls
4–5	238	214	3·0 ± 0·49	2·9 ± 0·54	3·0 ± 0·43
6–7	338	354	2·7 ± 0·56	2·7 ± 0·55	2·8 ± 0·58
8–9	264	275	2·7 ± 0·50	2·7 ± 0·54	2·6 ± 0·46
10–11	373	343	2·7 ± 0·50	2·6 ± 0·51	2·7 ± 0·47
12–13	402	462	2·7 ± 0·53	2·6 ± 0·56	2·7 ± 0·50
14–15	198	174	2·8 ± 0·48	2·8 ± 0·51	2·8 ± 0·44

Coefficient of regression on age, with standard error:
Total .. .. −0·02 ± 0·003 per year of age
Boys .. .. −0·02 ± 0·005 „ „ „ „
Girls .. .. −0·01 ± 0·004 „ „ „ „

DISCUSSION

It seems unlikely from these data that an increased intermetatarsal angle can cause an increase in hallux valgus, since hallux valgus shows its greatest increase before the age of 14, and intermetatarsal angle after the age of 15. There is no bimodal distribution of intermetatarsal angle in children which could lead us to pick out a group who would be likely to develop symptomatic bunions later in life. As the incidence of hallux valgus is unknown in the adult population, neither the 4 feet in children with an intermetatarsal angle >15° nor the 11 feet with hallux valgus >28° can be regarded as premorbid groups of a "threshold" variety. In view of the high correlation (coefficient 0·7) between hallux valgus and intermetatarsal angle in adult controls—still higher in the morbid group—it is difficult not to conclude that they are causally related, but that the

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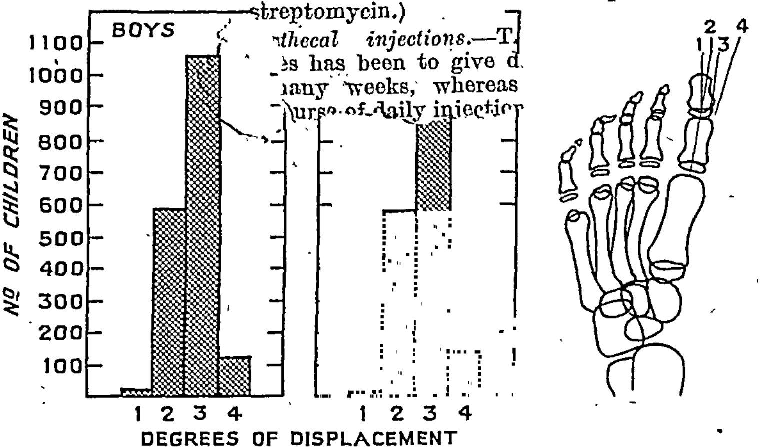

Fig. 3—Distribution of displacement of terminal phalanx of great toe, measured in arbitrary degrees.

TABLE IV—COMPARISON OF MEAN VALUES IN THE DIFFERENT SERIES

—	Series	Total no. of feet	Mean value and standard deviation		Series compared	Mean difference and its standard error		Significance
Degree of hallux valgus	Children (aged 4–5)	452	10·0°	± 4·4°	Adult controls and children (14–15)	0·6°	± 0·15°	Not significant
	Children (aged 14–15)	376	14·4°	± 4·9°				
	Adult controls	252	15·0°	± 6·4°	Adult controls and children (4–5)	5·0°	± 0·41°	Very highly significant
	Morbid group (hallux valgus)	165	32·0°	± 9·5°				
Inter-metatarsal angle	Children (aged 4–5)	452	7·4°	± 2·2°	Adult controls and children (14–15)	1·5°	± 0·20°	Very highly significant
	Children (aged 14–15)	376	7·6°	± 2·0°				
	Adult controls	252	9·1°	± 3·1°	Adult controls and children (4–5)	1·7°	± 0·20°	Very highly significant
	Morbid group (hallux valgus)	177	14·0°	± 4·1°				
Terminal phalanx displacement	Children (aged 4–5)	452	3·0°	± 0·49	Adult controls and children (14–15)	0·0°	±0·06	Not significant
	Children (aged 14–15)	372	2·8°	± 0·48				
	Adult controls	166	2·8°	± 0·87	Adult controls and children (4–5)	0·2°	± 0·06	Very highly significant
	Morbid group (hallux valgus)	152	2·3°	± 0·68				

displacement of the great toe is primary and causes the widening of the intermetatarsal angle.

There remains the question: what causes the displacement of the great toe in the first place?

There is in children a marked lateral displacement of the terminal phalanx upon the proximal; it is higher in the 4–5 age-group than in the 14–15, higher in children than in adults, and higher in all groups together (except the morbid one) than in the morbid group itself. At no age is there a significant positive correlation between this displacement and the lateral displacement of the whole toe—i.e., hallux valgus. It would be possible to argue that the displacement of the terminal phalanx tipped the balance in the first instance, but was immediately obliterated when the proximal phalanx was displaced from the longitudinal axis of the first metatarsal. This seems a far-fetched defence of a hypothesis which cannot well be substantiated without reference to the occurrence of hallux valgus in the habitually barefoot. Data from barefoot peoples are, in fact, of such crucial importance in this inquiry that we quote two pieces of evidence which are of a significance out of all proportion to their numerical size.

Footprints, which give an adequate objective measurement of hallux valgus (though of almost nothing else), personally communicated from the north-east Transvaal show hallux valgus of a fully pathological degree in two women who had never worn shoes. This condition is said to be not uncommon among the women of the tribes in that area. Hallux valgus can therefore occur among barefoot people, though in what proportion and with what symptoms is not known.

A condition of hallux varus is also recorded among the Annamites of French Indochina (Huard and Bigot 1943, Do-Xuan-Hop 1944). This condition, known as *giao-chi*, occurs in both sexes and consists of an angular displacement of the great toe medially for as much as 90°. It is also said to be associated with a widened intermetatarsal angle.

This evidence, slender though it may be, suggests that the factors influencing the position of the great toe must be sought elsewhere than in skeletal patterns and ill-designed footwear, though the rôle of the latter in producing symptoms is hard to deny. Little is known of the function of the abductor hallucis muscle, but it is clear that it urgently requires investigation.

SUMMARY

Evidence from standard radiographs of the feet of 1851 school-children suggests that the deformity of hallux valgus precedes widening of the first intermetatarsal angle.

A congenital widening of the intermetatarsal angle may not be as important in hallux valgus formation as has been thought.

The coefficient of correlation is an expression of the scatter of the plots of two variables on a correlation diagram. If the variables are independent the correlation coefficient will be zero; if the relationship is linear the coefficient will be ±1, the positive sign indicating a rise in the slope of the line joining the plots of ordinates and abscissæ, and a negative sign a fall. Intermediate values of the coefficient indicate the degree of approximation to a linear relationship. The coefficient of regression is an estimate of the slope of the line joining the plots of two variables on a correlation diagram.

We wish to thank Prof. J. Z. Young, F.R.S., for his helpful criticism; the Shoe and Allied Trades Research Association for the grant which paid for the work; Dr. W. G. Booth, medical officer of health, Area 7, Middlesex County Council, who made the inquiry possible, and his assistant, Dr. D. A. Craigmile; the headmasters and headmistresses of the schools concerned for their coöperation; and all others who were inconvenienced by our inquiry. We are particularly indebted to Mr. P. Venning, M.S.R., for his radiographic work. Mr. N. A. Barnicot drew attention to the Annamites, and Mr. Bancroft-Clark lent the footprints collected by Mrs. E. Krige in north-east Transvaal.

REFERENCES

Do-Xuan-Hop (1944) *Trav. Inst. anat. Fac. Méd. Indochine*, 8, 1.
Emslie, M. (1939) *Lancet*, ii, 1261.
Hardy, R. H., Clapham, J. C. R. (1951) *J. Bone Jt Surg.* 33B, 376.
Harris, R. I., Beath, T. (1947) Army Foot Survey, Ottawa.
Huard, P., Bigot, A. (1943) *Trav. Inst. anat. Fac. Méd. Indochine*, 2, 51.
Venning, P., Hardy, R. H. (1951) *Brit. J. Radiol.* 24, 18.

ACUTE SORE THROAT

CLINICAL FEATURES, ÆTIOLOGY, AND TREATMENT

J. M. Bishop
M.B. Birm.

A. S. Peden
M.B. Edin.

T. A. J. Prankerd
M.D. Lond., M.R.C.P.

From the Medical Division, Military Hospital, Tidworth

R. H. Cawley
B.Sc., Ph.D. Birm.

Acute sore throat is common in temperate climes and causes much loss of working capacity. It is therefore important to discover a form of treatment which is at once effective and economical.

Some observers have reported benefit from sulphonamides, taken by mouth or insufflated into the throat (Freis 1944, Goldman and Kiesewetter 1946), and large quantities of these drugs are used in this way. Other investigators, however, think that their value has not been proved (Rhoads and Afremow 1940, Anderson 1949, Macdonald and Watson 1951). Penicillin has given uniformly good results when administered systemically (Plummer et al. 1945), but is of little value in lozenges or pastilles.

In this paper the term "sore throat" means an illness in which this is the predominant symptom, visible inflammation in the fauces and pharynx is the principal sign, and no other malady is detected. This defines a group of cases excluding abortive forms of the common cold, influenza, glandular fever, and other blood diseases, and the infectious fevers. The term "sore throat" is preferred to "tonsillitis" because this implies organs often absent, and to "pharyngitis" because this implies a restricted location.

The primary object of our investigation was to test the efficacy of three schemes of treatment, and the cases investigated comprised 120 consecutive admissions to Tidworth Military Hospital between October, 1950, and April, 1951, of cases of acute sore throat as defined. The patients were all males, and the age-distribution was:

Age (yr.) ..	15–19	20–24	25–29	30–34	35–39	40–44	45–49
No. of cases ..	68	38	8	1	3	1	1

METHOD OF INVESTIGATION

Examination

Each patient on admission underwent complete physical examination, particular attention being paid to the throat and jugulodigastric lymph-nodes. The degree of œdema, erythema, and exudate on tonsils and fauces, and of enlargement and tenderness of the local lymph-nodes, were estimated on a quantitative scale from 0 to ++++. Since the large majority of patients were examined by one of us (J. M. B.), the standards remained fairly constant.

TABLE I—BACTERIOLOGY AND TREATMENT

Bacteriological group	No. of cases	Treatment		
		Penicillin	Sulphonamide	Controls
Streptococcal ..	49	13 (*26%*)	19 (*39%*)	17 (*35%*)
Commensal ..	66	26 (*39%*)	20 (*30%*)	20 (*30%*)
Total ..	115	39 (*34%*)	39 (*34%*)	37 (*32%*)

Immediately after examination a throat swab was taken on dry cotton-wool swabs and cultured on Loeffler's medium and on blood-agar. A differential white-cell count was made and the urine examined.

Physical examination was repeated daily, and the temperature and pulse-rate were recorded twice daily. In 29 cases a throat swab was taken twenty-four hours after the start of treatment, and in all cases a throat swab was taken on discharge from hospital. Wherever the clinical condition or blood picture suggested glandular fever several white-cell counts and Paul-Bunnell tests were made.

In 111 of the 120 cases the patient was seen a month after discharge. At this interview he was questioned about recurrence of sore throat and particularly about any symptoms of rheumatic fever or nephritis. He was then examined, a further throat swab was taken, and the urine was tested.

TABLE II—SEVERITY OF INFECTION IN RELATION TO BACTERIOLOGICAL GROUP

Bacteriological group	Mild	Severe
Streptococcal ..	27 (*55%*)	22 (*45%*)
Commensal ..	54 (*82%*)	12 (*18%*)
Total ..	81 (*70%*)	31 (*30%*)

Treatment

The patients were allotted to treatment groups in rotation according to their order of admission. Where an exceptionally severe case fell in the control group and it was felt unjustifiable to withhold specific treatment, the case was transferred to one of the other groups and the next case was placed in the control group. The effect of this was to load the penicillin and the sulphadimidine groups equally with more *exceptionally severe* cases than would have occurred by chance. The number of such cases was in fact very small.*

The patients remained in bed during treatment and had the usual hospital diet with copious fluid. They all received hot phenol gargles (Gargarisma phenolis *B.P.C.*) and aspirin gr. $7^1/_2$ (in the form of mist. acidi acetylsalicylici *B.P.C.* $^1/_2$ oz.) every four hours.

The *control group* received no additional treatment.

The *penicillin group* received in addition on each of four days an injection of procaine penicillin in arachis oil with 2% aluminium monostearate containing 300,000 units of penicillin.

The *sulphadimidine group* received in addition sulphadimidine in an initial dose of 2 g. followed by 1 g. four-hourly to a total of 20 g.

The patients were allowed up as soon as their temperature had been normal for twenty-four hours and the throat had returned to normal. They were discharged from hospital after they had been up for a whole day and had remained well.

FINDINGS

Distribution of Cases

Of the 120 cases studied 3 were diagnosed as glandular fever and 2 as Vincent's angina. These are excluded from further consideration, leaving 115 cases. From a bacteriological point of view the latter were divided into two groups: (1) those yielding a predominant growth of β-hæmolytic streptococci on culture (*streptococcal group*), and (2) those from which no predominant organism was

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* The bias entailed in such transference would tend to give an unduly favourable view of the results of control treatment, and thereby to diminish the differences between responses to antibiotic or drug and control treatment. The bias was in fact negligible because the proportion of cases transferred was very low.

TABLE III—CLINICAL MANIFESTATIONS IN STREPTOCOCCAL AND COMMENSAL GROUPS

Clinical sign or symptom	Streptococcal group (49 cases)	Commensal group (66 cases)	Difference (%)	t	P (where 0·05 or less)
Duration of sore throat before admission less than 24 hours ..	31 (*63·3%*)	29 (*43·9%*)	+19·4	2·06	0·02–0·05
Maximum temperature 100°F or over ..	34 (*69·4%*)	39 (*59·1%*)	+10·3	1·13	..
Maximum pulse-rate over 100 ..	9 (*18·4%*)	16 (*24·2%*)	−5·8	0·75	..
Œdema of tonsils and fauces moderate or severe ..	24 (*49·0%*)	20 (*30·3%*)	+18·7	2·04	0·02–0·05
Erythema of tonsils and fauces moderate or severe ..	41 (*83·7%*)	47 (*71·2%*)	+12·5	1·56	..
Exudate on tonsils and fauces copious ..	19 (*38·8%*)	11 (*16·7%*)	+22·1	2·67	0·01–0·001
No exudate on tonsils or fauces ..	7 (*14·3%*)	20 (*30·3%*)	−16·0	2·00	0·05
Jugulodigastric lymph-nodes much enlarged ..	16 (*32·7%*)	9 (*13·4%*)	+19·3	2·44	0·01–0·02
Much [illegible] lymph-nodes ..	15 (*30·6%*)	8 (*11·9%*)	+18·7	2·43	0·01–0·02
Œdem [illegible] severe ..	8 (*17·0%*)	15 (*24·6%*)	−7·6	0·96	..
Erythema of pharynx* moderate or severe ..	35 (*74·5%*)	46 (*75·4%*)	−0·9	0·11	..
Exudate of pharynx* moderate or copious ..	13 (*27·7%*)	18 (*29·5%*)	−1·8	0·21	..
Fetor oris present ..	18 (*36·7%*)	19 (*28·8%*)	+7·9	0·90	..

* Based on an examination of 47 cases and 61 cases in streptococcal and commensal groups respectively.

t, difference ÷ standard deviation of difference.

P, probability of stated difference occurring by chance.

isolated (*commensal group*). No case of diphtheria was encountered.

The distribution of cases according to bacteriology and treatment is shown in table I. There is no undue bias in allocation of cases to treatment groups ($\chi^2 = 2{\cdot}12$, $P = 0{\cdot}3$–$0{\cdot}5$).

An arbitrary classification was also made according to the severity of the infection, two grades being recognised—mild and severe. The following seven factors were considered:

(1) Duration of sore throat on admission: twenty-four hours or less.

(2) Highest temperature: 101°F or more.

(3) Presence of considerable œdema of fauces (++).

(4) Presence of considerable erythema of fauces (++).

(5) Presence of moderate degree (+) or greater of exudate on tonsils or fauces.

(6) Presence of moderate degree (+) or greater of enlargement of jugulodigastric glands.

(7) Presence of a moderate degree (+) or greater of tenderness of jugulodigastric glands.

Where four or more of the factors were present the case was regarded as severe; where there were less than four it was classified as mild.

The distribution of cases, thus classified, is shown in table II, from which it will be seen that a much larger proportion of streptococcal than commensal infections were severe (45% against 18%; $\chi^2 \doteq 9{\cdot}60$, $P = 0{\cdot}01$–$0{\cdot}001$). It will also be seen that some 65% of severe cases were in the streptococcal group, whereas some 67% of mild cases were in the commensal group.

Correlation of Clinical Features with Bacteriological Group

Table III shows the incidence of signs and symptoms in the two bacteriological groups. Only in the following respects are the differences statistically significant:

(1) *Exudate on tonsils and fauces* was copious in 39% of the streptococcal group and 17% of the commensal group. This difference is very unlikely to be due to chance. Absence of faucial exudate was more often recorded in the commensal group, but this excess is less reliable statistically. The character of the exudate was not useful as a diagnostic point, but a confluent purulent exudate was often observed in the streptococcal group.

(2) *Enlargement and tenderness of jugulodigastric lymph-nodes* were both considerable, with significantly higher frequencies in the streptococcal group.

(3) *Duration of sore throat* on admission was less than twenty-four hours in 63% of the streptococcal cases and only 44% of the commensal group. This difference appears to be significant and suggests that the illness was of more acute onset in the streptococcal cases.

(4) *Œdema of fauces* was moderate or severe slightly more often in the streptococcal group than in the commensal group.

These differences do not seem clear enough to enable the clinician to recognise the bacteriological group with any certainty.

TABLE IV—BACTERIOLOGICAL EXAMINATIONS OF STREPTOCOCCAL GROUP

Time of examination	No. of cases in which β-hæmolytic streptococci were absent, according to treatment group		
	Penicillin	Sulphadimidine	Control
At 24 hours..	3 out of 10 *(30%)*	0 out of 11	0 out of 8
On discharge	11 out of 13 *(85%)*	9 out of 18 *(50%)*	14 out of 19 *(74%)*
At follow-up	12 out of 13 *(92%)*	14 out of 16 *(88%)*	11 out of 13 *(84%)*

Pathology

As noted above, a predominant growth of β-hæmolytic streptococci was obtained from the throat swabs in 49 (43%) of the cases. Of these, 45 (92%) were of Lancefield group A, 3 (6%) group C, and 1 (2%) group G.

An attempt was made to follow the speed of disappearance of β-hæmolytic streptococci from the throat under the three forms of treatment; the results obtained are shown in table IV.

A total white-cell count greater than 11,000 per c.mm. was found in 28 (57%) of the streptococcal group and 27 (41%) of the commensal group. A count of over

TABLE V—RESULTS OF TREATMENTS IN COMMENSAL AND STREPTOCOCCAL GROUPS

Treatment	Commensal group								Streptococcal group							
	Duration of fever (days)		Tonsils and fauces abnormal (days)		Lymph-glands tender (days)		Stay in hospital (days)		Duration of fever (days)		Tonsils and fauces abnormal (days)		Lymph-glands tender (days)		Stay in hospital (days)	
	No.	Mean ± S.D.	No.	Mean ± S.D.	No.	Mean ± S.D.	No.	Mean ± S.D.	No.	Mean ± S.D.	No.	Mean ± S.D.	No.	Mean ± S.D.	No.	Mean ± S.D.
1. Penicillin	24	1·63 ±0·23	26	3·46 ±0·22	26	1·96 ±0·28	26	5·35 ±0·18	13	1·69 ±0·17	13	3·23 ±0·29	13	2·31 ±0·33	13	5·08 ±0·20
2. Sulphadimidine	20	1·95 ±0·27	20	3·55 ±0·25	20	2·30 ±0·38	20	5·75 ±0·22	19	2·16 ±0·28	19	3·32 ±0·26	19	3·11 ±0·39	19	6·42 ±0·44
3. Control.	19	2·58 ±0·58	20	3·80 ±0·79	20	2·20 ±0·59	20	6·40 ±0·78	17	2·35 ±0·42	17	4·41 ±0·47	17	3·12 ±0·51	17	6·41 ±0·37
Comparisons:																
Penicillin-sulphadimidine																
Difference: (1) minus (2)		−0·32		−0·09		−0·34		−0·40		−0·47		−0·09		−0·80		−1·34
t ..		0·90		0·85		0·72		1·41		1·43		0·73		1·54		2·77
P (where 0·05 or less) ..		..		..		..		..		..		..		..		≃0·01
Penicillin-control																
Difference: (1) minus (3)		−0·95		−0·34		−0·24		−1·05		−0·66		−1·18		−0·81		−1·33
t ..		1·52		0·41		0·37		1·31		1·46		2·14		1·33		3·16
P (where 0·05 or less) ..		..		..		..		..		..		0·02–0·05		..		0·001–0·0
Sulphadimidine-control																
Difference: (2) minus (3)		−0·63		−0·25		+0·10		−0·65		−0·19		−1·09		−0·01		+0·01
t ..		0·97		0·30		0·14		0·80		0·38		2·03		0·02		0·02
P (where 0·05 or less) ..		..		..		..		..		..		≃0·05		..		..

15,000 per c.mm. was found in 18 (37%) of the streptococcal group and 11 (17%) of the commensal group.

Sensitivity tests to penicillin of the isolated streptococci and estimations of blood-penicillin levels were omitted; the former because the β-hæmolytic streptococcus of group A is fully sensitive to penicillin and its acquired resistance to this antibiotic unknown, and the latter because adequate blood-penicillin levels up to twenty-six hours after injection have been demonstrated by other investigators (Jones and Shooter 1948, Garrod 1950, 1951).

Results of Treatment

As soon as an attempt is made to assess response to treatment, difficulty arises as to which criteria best indicate clinical improvement. In this paper four have been adopted: (1) duration of fever; (2) duration of faucial abnormality; (3) duration of tenderness of jugulodigastric lymph-nodes; and (4) duration of stay in hospital. As throughout the investigation the same rules were applied to discharge from hospital, we consider that the last criterion is of true value and gives the best single estimate of the efficacy of treatment.

The results of treatment in the streptococcal and commensal groups are given in table v. It is evident that for the commensal group there is no significant difference in response to treatment by any of the three schemes. In the streptococcal group the most significant differences lie in duration of stay in hospital, a reduction of a sixth being obtained when penicillin is used, compared with either sulphadimidine or control treatment. A significant shortening of the duration of faucial abnormality is found when penicillin is used rather than control treatment, and a reduction of the same order is also observed with sulphadimidine.

As a confident clinical diagnosis of the bacteriological group cannot be made, the practical value of a comparison of streptococcal with commensal groups is somewhat limited. We have therefore compared the response to treatment of cases falling in the two clinical subdivisions of mild and severe, and the results are shown in table VI.

For *mild* cases a significant but not large reduction of duration of stay in hospital was found when both the penicillin and sulphadimidine, and penicillin and control groups were compared. Treatment with sulphadimidine did not give any better results than control treatment.

Comparison within the *severe* group is more difficult, because the control-treated cases form a heterogeneous group, and the standard deviation of the mean is consequently large. Nevertheless it will be seen that penicillin, compared with control treatment, substantially shortens the stay in hospital, and also reduces the duration of faucial abnormality and tenderness of tonsillar glands. The effect of treatment with sulphadimidine is less striking, the only significant difference being in the duration of faucial abnormality. When penicillin is compared with sulphadimidine, no significant difference is found, although in all criteria, except duration of faucial abnormality, the response favours the former.

Complications and Relapses

The effect of treatment may also be compared by a study of relapses and of complications. 3 relapses were seen within a week of cessation of treatment; 2 of the patients had been treated with sulphadimidine, and 1 as a control.

Complications were remarkably few, there being 1 case of otitis media and 1 of acute nephritis. Both had been treated with sulphadimidine, and both had shown β-hæmolytic streptococci predominantly during the illness.

DISCUSSION

The patients who formed this series were previousl healthy young men. Hence our conclusions cannot b applied to the general population without reservations

The finding of a predominant growth of β-hæmolytic streptococci on culture in 43% of the cases i comparable to the findings of previous investigator (Commission on Acute Respiratory Diseases 1944 1945). No other predominant organism was isolate from these cases on admission which was not also foun

TABLE VI—RESULTS OF TREATMENTS IN MILD AND SEVERE GROUPS

Treatment	Mild group								Severe group							
	Duration of fever (days)		Tonsils and fauces abnormal (days)		Lymph-glands tender (days)		Stay in hospital (days)		Duration of fever (days)		Tonsils and fauces abnormal (days)		Lymph-glands tender (days)		Stay in hospital (days)	
	No.	Mean ± S.D.	No.	Mean ± S.D.	No.	Mean ± S.D.	No.	Mean ± S.D.	No.	Mean ± S.D.	No.	Mean ± S.D.	No.	Mean ± S.D.	No.	Mean ± S.D.
1. Penicillin	29	1·48 ±0·16	31	3·13 ±0·17	31	2·03 ±0·25	31	5·06 ±0·12	9	2·22 ±0·34	9	4·44 ±0·47	9	2·33 ±0·42	9	5·78 ±0·41
2. Sulphonamide	22	2·05 ±0·28	22	3·41 ±0·24	22	2·36 ±0·34	22	5·77 ±0·16	17	2·18 ±0·24	17	3·47 ±0·28	17	3·12 ±0·45	17	6·47 ±0·52
3. Control.	28	2·07 ±0·33	29	3·17 ±0·32	29	2·07 ±0·39	29	5·66 ±0·27	8	3·88 ±1·01	8	7·38 ±1·39	8	4·75 ±0·93	8	9·13 ±1·51
Comparisons:																
Penicillin-sulphadimidine																
Difference: (1) minus (2)		−0·57		−0·28		−0·33		−0·71		+0·04		+0·97		−0·79		−0·69
t ..		1·77		0·95		0·78		2·8		0·10		1·77		1·28		1·04
P (where 0·05 or less) ..		..		..		..		0·001–0·01		..		..		..		..
Penicillin-control																
Difference: (1) minus (3)		−0·59		−0·04		−0·04		−0·60		−1·66		−2·94		−2·42		−3·35
t ..		1·61		0·35		0·09		2·03		1·55		2·00		2·37		2·15
P (where 0·05 or less) ..		..		..		..		≃0·05		..		≃0·05		0·02–0·05		≃0·05
Sulphadimidine-control																
Difference: (2) minus (3)		−0·02		+0·24		+0·29		+0·11		−1·70		−3·91		−1·63		−2·66
t ..		0·05		0·60		0·56		0·35		1·63		2·75		1·58		1·66
P (where 0·05 or less) ..		..		..		..		..		..		≃0·01		..		..

frequently in the follow-up. We do not believe, therefore, that other organisms, such as *Strep. viridans* and *Strep. pneumoniæ*, played any causal rôle in the sore throats of these cases.

β-hæmolytic streptococci cannot be considered causal in all our cases in which they were present. Studies by the Commission on Acute Respiratory Diseases (1944, 1945) reveal that in half the cases of acute sore throat from throat swabs of which β-hæmolytic streptococci were isolated there was no subsequent rise in anti-streptolysin titre. Such a rise in titre is considered to take place almost invariably after infection with the β-hæmolytic streptococcus, and it is therefore suggested that in those cases in which a rise does not take place the illness is the result of a non-specific infection in a carrier of the organism. Accordingly the group labelled *streptococcal* cannot be regarded as homogeneous, and the clinical features and response to treatment will not be uniform. The difficulty of distinguishing streptococcal and non-streptococcal cases clinically has been emphasised by the Commission on Acute Respiratory Disease (1944, 1945, 1947) and Landsman et al. (1951), and our findings agree closely with theirs. Probably physicians seeing large numbers of such cases will be able to make a clinical diagnosis with more confidence, and Rantz et al. (1946a) claim accuracy in 70% of cases.

The form of treatment used for the commensal group is evidently immaterial; but for the streptococcal group penicillin substantially shortens stay in hospital, compared with either sulphadimidine or control treatment. Since it is hardly possible to make a certain diagnosis of the bacteriological group, we attach more importance to a comparison between *mild* and *severe* cases—an easy differentiation made on purely clinical grounds.

Such a comparison shows that for the mild group a significant shortening of stay in hospital is produced by penicillin, but its degree is hardly great enough to justify the use of the antibiotic. Consideration of the severe group shows that penicillin produces a large and significant reduction in hospital stay compared with control treatment, whereas sulphadimidine does not produce a significant shortening.

2 of the 3 observed relapses and the only 2 notable complications occurred in sulphadimidine-treated cases. No relapse or complication was seen in a patient treated with penicillin; this is probably related to the more rapid disappearance of streptococci from the throat. Sulphadimidine produced no more rapid clearing than did symptomatic treatment.

The findings of Rantz et al. (1946b), suggested that adequate treatment with penicillin reduced the frequency of rising anti-streptolysin titre. Since rheumatic fever is closely related to a high anti-streptolysin titre, it is possible that penicillin treatment of streptococcal sore throats might reduce the incidence of this complication.

From our data we conclude that, as a guide to treatment, cases of acute sore throat should be classified as either severe or mild. Mild cases may be effectively treated with symptomatic measures such as hot gargles and aspirin. Severe cases should receive four days' penicillin treatment, daily injections of a preparation of procaine penicillin being effective.

In our series sulphadimidine was not seen to be beneficial in cases of the normal range of severity. Owing to the unavoidable bias in our sample (see above) we cannot assess its usefulness in cases of exceptional severity: but, since it occasionally produces undesirable or even serious ill effects, we consider its use to be unjustifiable in the treatment of sore throat.

Clearly, bacteriological examination of the throat will be required in those patients who have had a previous attack of rheumatic fever and in those in whom there is a clinical suspicion of diphtheria.

SUMMARY

A series of 115 cases of acute sore throat is presented. β-hæmolytic streptococci were cultured from the throat swabs of 43%.

Streptococcal infections were not so distinctive in their signs and symptoms that they could be recognised with any certainty in the absence of bacteriological examination.

So far as treatment is concerned, a clinical classification according to severity is of more practical value than a bacteriological one; but a throat swab must be taken if there is a history of rheumatic fever or a possibility of diphtheria.

Mild cases respond to symptomatic treatment but in severe cases penicillin shortens the illness. In our series no benefit was apparent from the use of sulphadimidine, and its use is considered unjustifiable.

We wish to record our gratitude to Prof. W. Melville Arnott for helpful criticism, to the Director-General of Army Medical Services for permission to publish, and to Lieut.-Colonel C. A. Slaughter, R.A.M.C., officer commanding Military Hospital, Tidworth. Private L. Goulding, R.A.M.C., gave valuable technical assistance.

REFERENCES

Anderson, T. (1949) *Brit. med. J.* ii, 860.
Commission on Acute Respiratory Diseases (1944) *J. Amer. med. Ass.* 125, 1163.
— (1945) *Amer. J. Publ. Hlth*, 35, 675.
— (1947) *J. Amer. med. Ass.* 133, 588.
Freis, E. D. (1944) *Ibid*, 126, 93.
Garrod, L. P. (1950) *Brit. med. J.* ii, 617.
— (1951) *Ibid*. i, 205.
Goldman, J. L., Kiesewetter, W. B. (1946) *Arch. Otolaryngol.* 43, 99.
Jones, P. F., Shooter, R. A. (1948) *Brit. med. J.* ii. 933.
Landsman, J. B., Grist, N. R., Black, R., McFarlane, D., Blair, W., Anderson, T. (1951) *Ibid*, i. 326.
Macdonald, T. C., Watson, I. H. (1951) *Ibid*. p. 323.
Plummer, N., Duerschner, D. R., Warren, H. D., Rogliano, F. T., Sloan, R. A. (1945) *J. Amer. med. Ass.* 127, 369.
Rantz, L. A., Boisvert, P. J., Spink, W. W. (1946a) *Arch. intern. Med.* 78, 369.
— — — (1946b) *Science*, 103, 352.
Rhoads, P. S., Afremow, M. L. (1940) *J. Amer. med. Ass.* 114, 942.

RESIDUAL PARALYSIS AFTER POLIOMYELITIS FOLLOWING RECENT INOCULATION

BERTRAM P. McCLOSKEY
M.D. Melb.

POLIOMYELITIS OFFICER, STATE HEALTH DEPARTMENT,
VICTORIA, AUSTRALIA

DURING the epidemic of poliomyelitis in Victoria, Australia, in 1949–50 it was observed that a small proportion of patients with paralysis had a recent history of inoculation, usually with pertussis vaccine (McCloskey 1950, 1951). Similar observations have been made in Great Britain and North America (Geffen 1950, Hill and Knowelden 1950, Banks and Beale 1950, Anderson 1951). As paralysis in recently inoculated limbs is usually severe, the purpose of the present inquiry was to ascertain whether there is less chance of recovery in these cases of poliomyelitis following inoculation than there is in other cases of poliomyelitis of similar severity.

THE INVESTIGATION

Material

As most of the cases of paralysis following inoculation were in children under three years old, the inquiry was confined to this age-group. Of 675 cases of poliomyelitis notified from January to November, 1949, 118 were in children aged three years or less. Of these, 28 have been excluded: 5 in whom recent inoculation was doubtful; 4 because of some discrepancy in the immunisation record; 4 because of incomplete records; and 15 in whom no extremity was paralysed. This report concerns the remaining 90 children, 25 of whom had received an immunising injection within thirty days of the onset of symptoms, and 65 had not.

TABLE I—RESIDUAL PARALYSIS AFTER EIGHTEEN MONTHS IN PATIENTS INOCULATED WITHIN THIRTY DAYS OF ONSET OF POLIOMYELITIS AND IN 65 PATIENTS NOT SO INOCULATED

Patients recently inoculated	Initial paralysis	No. of extremities	Residual paralysis at 18 months				
			Very severe	Severe	Moderate	Slight	Nil
Yes	Very severe	13	0	3	4	4	2
No	,, ,,	12	0	4	7	1	0
Yes	Severe	9	..	0	0	6	3
No	,,	16	..	0	5	9	2
Yes	Moderate	7	..	..	0	0	7
No	,,	22	..	..	3	8	11
Yes	Slight	9	..	..	..	0	9
No	,,	57	..	..	..	8	49

Methods of Treatment

In Victoria the cost of treatment for patients with poliomyelitis, including physiotherapy, is paid by the State government, in association with the committees of public hospitals. Children under three are treated in recumbency, usually on the Macnamara frame, until they have completely recovered or attained maximal benefit. Specific splinting for paralysed extremities is used where indicated. Muscle re-education is undertaken when the child is old enough to coöperate. Substitution movements are not taught or encouraged during the convalescent phase. Hot packs are not used, but saline baths are given for stiffness or muscle pain. Particular attention is given to the prevention of deformities.

Assessment of Site and Severity of Paralysis

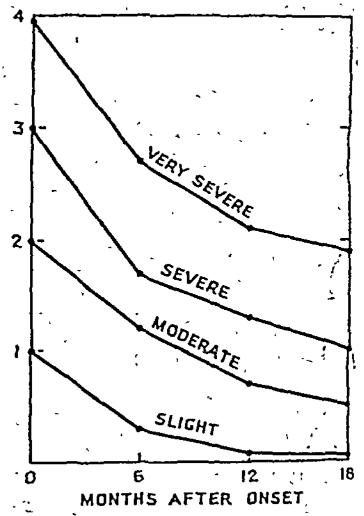
The sites and the severity of paralyses were determined at the first examination or very soon after the diagnosis had been established. The majority of patients were assessed initially by me, the remainder by physicians experienced in treatment of poliomyelitis. All assessments were checked with the records of the physiotherapists treating the patients. Progress examinations were made at intervals of six, twelve, and eighteen months from the onset of symptoms. The extent of paralysis, recorded in the case-notes according to the standard scale of the Australian Association of Physiotherapists, has been converted for the purpose of this report into the following gradings:

4. *Very severe.*—Complete flaccid paralysis of the extremity.
3. *Severe.*—Complete paralysis of at least one muscle group.
2. *Moderate.*—Partial paralysis of at least one muscle group not permitting movement of the involved joint against gravity.
1. *Slight.*—Lesser degrees of paralysis permitting movemen against gravity.
0. *Nil.*—No detectable paralysis.

This grading is relatively coarse, and no differentiatio has been made between paralysis of upper and lowe extremities. The material is insufficient for close analysis.

Findings

Eighteen months after the onset the proportion o extremities showing no residual paralysis was the sam in patients in the recently inoculated group as in patient not recently inoculated (21 out of 38 compared to 6 out of 107). Such a comparison does not take int account the fact that the degree of initial paralysi varied in the two groups of children. Table I shows tha in the recently inoculated patients, the initial paralysi was maximal in 13 of 38 affected limbs, compared to 1 of 107 in children not recently inoculated. (In the 26 extremities last inoculated before onset, the paralysis was very severe in 12, and severe in 7.)



Recovery-rate of 145 extremities in 90 children, according to severity of initial paralysis.

If, on the other hand, the comparison at eighteen months is made between those extremities initially paralysed in he same degree, the recently inoculated patients show a slight advantage in every grading. For example, in recently inoculated children 2 out of 13 extremities initially graded *very severe* showed no residual paralysis at eighteen months compared to 0 out of 12 in the not-inoculated group. Corresponding figures for *severe* initial paralyses were 3 out of 9 and 2 out of 16. However, when all gradings are combined the slight differences between the two groups in the degree of recovery at eighteen months are not significant statistically ($n = 4, \chi^2 = 5{\cdot}13, p > 0{\cdot}20$). It is therefore concluded that there is no significant difference in the extent of recovery of extremities initially paralysed to the same degree in children under three who had and had not been recently inoculated.

TABLE II—RECOVERY OF PARALYSIS IN RELATION TO SEVERITY AT ONSET, IN 145 EXTREMITIES OF 90 CHILDREN (25 RECENTLY INOCULATED AND 65 NOT INOCULATED)

—	Very severe	Severe	Moderate	Slight	Nil	Average*
Onset ..	25	..	..	..	..	4·0
6 months ..	1	16	8	0	0	2·7
12 ,, ..	0	8	12	5	0	2·1
18 ,, ..	0	7	11	5	2	1·9
Onset ..	..	25	..	..	..	3·0
6 months ..	..	2	14	8	1	1·7
12 ,, ..	..	0	11	10	4	1·3
18 ,, ..	..	0	5	15	5	1·0
Onset ..	..	..	29	..	..	2·0
6 months ..	..	..	8	18	3	1·2
12 ,, ..	..	..	3	13	13	0·7
18 ,, ..	..	..	3	8	18	0·5
Onset ..	..	..	..	66	..	1·0
6 months ..	..	..	..	18	48	0·3
12 ,, ..	..	..	..	9	57	0·1
18 ,, ..	..	..	..	8	58	0·1

* Average paralysis calculated by scoring each extremity according to the scale: *Nil* 0, *slight* 1, *moderate* 2, *severe* 3, *very severe* 4.

PROSPECTS OF RECOVERY

In view of this conclusion, I have combined the data from both groups of children so as to obtain an over-all estimate of recovery in eighteen months under the methods of treatment used in Victoria.

Table II shows, as might be expected, that the more severe the initial paralysis the smaller is the chance of complete recovery. Of 25 extremities originally completely paralysed, only 2 (8%) recovered completely. But all showed some degree of recovery: 18 (72%) improved two grades or better; and the average score for the entire group at eighteen months was 1·9. (Each extremity is scored on a scale ranging from 4 points for *very severe* to 0 for *nil.*) Of 25 extremities severely paralysed at onset, 5 recovered completely; all showed some improvement (20 improving at least two grades), and the final average recovery was 1·0. Of 29 extremities with moderate paralysis at onset, 18 (62%) recovered completely, and of 66 with slight paralysis 58 (88%) recovered completely.

The over-all improvement in eighteen months was very substantial. Of the 145 extremities originally paralysed, only 11 (8%) showed no improvement. 83 (57%) recovered completely and in some of the others further improvement may be expected with continuance of treatment.

The rates of recovery in extremities paralysed initially in various degrees are compared graphically in the accompanying figure. The slopes of the curves indicating rates of improvement are roughly parallel in all grades.

SUMMARY

(1) The rate and extent of recovery has been assessed in paralysed extremities in 90 children under three years of age affected with poliomyelitis in the Victorian epidemic of 1949–50.

(2) A comparison was made between the recovery of 25 children whose poliomyelitis had followed recent inoculation and 65 children in whom there was no such history.

(3) The inoculated group contained a higher proportion of cases of severe paralysis; but, when cases of equal initial severity were compared, the residual paralysis after eighteen months was not significantly different in the two groups.

I am indebted to Dr. G. E. Cole, the chairman of the Health Commission, Victoria, for permission to publish this paper. I acknowledge gratefully the guidance and help given by me Dr. E. V. Keogh in the preparation of this paper. Also I wish to thank Dr. H. McLorinan of Fairfield Hospital, and Dr. V. L. Collins, of the Children's Hospital, for giving me access to the patients and their records, and Dame Jean Macnamara who has for many years trained physiotherapists in Victoria in the aftercare of poliomyelitis.

REFERENCES

Anderson, G. W., Skaar, A. E. (1951) *Pediatrics*, 7, 741.
Banks, H. S., Beale, A. J. (1950) *Brit. med. J.* ii, 251.
Geffen, D. H. (1950) *Med. Offr*, 83, 137.
Hill, A. B., Knowelden, J. (1950) *Brit. med. J.* ii, 1.
McCloskey, B. P. (1950) *Lancet*, i, 659.
—— (1951) *Med. J. Aust.* i, 613.

DOES ADRENALINE EOSINOPENIA REFLECT PITUITARY-ADRENAL FUNCTION IN MAN?

ROBERT M. KARK
M.R.C.P., F.A.C.P.

PROFESSOR OF MEDICINE, UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE; ATTENDING PHYSICIAN, RESEARCH AND EDUCATIONAL HOSPITALS, CHICAGO

ROBERT C. MUEHRCKE
B.S. Illinois

ARMOUR RESEARCH FELLOW IN MEDICINE, UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE, CHICAGO

IT is well known that a transitory eosinopenia may appear in healthy people after injection of small amounts of adrenaline or after treatment with ephedrine (Best et al. 1950, Abelson and Moyes 1950). These facts led to the development of four-hour eosinophil-response tests to parenteral adrenaline and oral ephedrine, which are widely used for estimating the functional activity and the integrity of the pituitary-adrenal system in man (Jailer et al. 1951, Solomon and Shock 1950, Roche et al. 1950, Smith 1950, Wolfson and Cohn 1950).

The adrenaline test, first used by Recant et al. (1950), is done by counting circulating eosinophils before, and four hours after, the injection of adrenaline 0·3 mg. A 50% decrease in the number of eosinophils is said to indicate normal activity of the pituitary or adrenal gland. Recant et al. (1950) suggested that the hypothalamus, pituitary, and adrenal cortex were successively stimulated by the adrenaline to produce first adrenocorticotropic hormone (A.C.T.H.), next adrenocortical hormone(s), and finally eosinopenia.

The eosinopenia of stress is also supposed to be mediated through this system. Apparently the adrenaline (sympathin) excreted from the adrenal medulla in fear, rage (Cannon and Rosenblueth 1937), and other types of psychological and physical trauma (Selye 1950) initiates release of A.C.T.H. from the pituitary, either by direct action or through the hypothalamus.

Recently, we and our colleagues have presented evidence (Best et al. 1951a and b, 1952) obtained by statistical analysis of a large number of eosinophil-response tests, which indicates that the adrenaline and ephedrine response tests are of little value in the diagnosis of adrenal, hypothalamic, or pituitary disease, and do not assess the functional capacity of these organs accurately.

We report here observations on patients who had undergone bilateral complete adrenalectomy, and were being maintained in health with cortisone, which indicate that adrenaline eosinopenia can be induced in the absence of the adrenal gland. On the basis of these observations and on observations reported elsewhere (Best et al. 1951b, Abelson and Moyes 1950, Almy et al. 1950) on patients with pituitary tumours, we doubt that adrenaline eosinopenia reflects pituitary-adrenal function in man.

MATERIAL AND METHODS

The Patients.—Three male patients were studied who had carcinoma of the prostate with metastases. Bilateral orchidectomy and a two-stage bilateral complete adrenalectomy were done as therapeutic measures. The operations on the three patients were done two weeks, three weeks, and five weeks before this study began. The patients were maintained in a eu-adrenal state by daily therapy with cortisone acetate, case 1 receiving cortisone 6·25 mg. at 6 A.M., noon, and 6 P.M., case 2 12·5 mg. at 6 A.M. and 6 P.M., and case 3 25 mg. at 6 A.M. and 6 P.M.

Technique of Testing.—Pre-treatment (zero-hour) venous blood for control eosinophil-counts was taken between 8.45 A.M. and 9 A.M., immediately after breakfast had been eaten. Medication was given at 9 A.M. and consisted of a subcutaneous injection of saline solution or of adrenaline 0·3 mg., or an intramuscular injection of potent tested A.C.T.H. (Armour) 40 mg. As we have shown that eosinophil responses to test materials may be inadequate if tests are done on successive days (Best et al. 1952), each test was separated from the next by at least four days.

After the injection the patients stayed quietly at their beds, and four hours later (at 1 P.M.) a second sample of venous blood was taken, luncheon having been eaten between noon and 12.30 P.M. The patients did not know what they were getting but reacted in the usual way to adrenaline.

Technique of Counting Eosinophils.—This is described in detail elsewhere (Best et al. 1952). In brief, the eosinophils are stained by the modification of Henneman et al. (1949) of Randolph's (1944) method, and for each sample of blood two leucocyte pipettes and eight Levy counting-chambers were used to obtain each count. Statistical significance was decided by reference to tables and charts published elsewhere (Best and Samter 1951, Best et al. 1952).

RESULTS AND DISCUSSION

During a study of three different eosinophil-response tests (Best et al. 1952), which were used as indices of activity of the pituitary gland or the adrenal cortex, observations were also made on five patients with tumours arising within, or infringing on, the sella turcica. These five patients were tested repeatedly with A.C.T.H. and with adrenaline. They gave a normal response to A.C.T.H., but their response to the adrenaline test, measured at the end of four hours, varied from a 24%

increase to a 65% decrease in the number of eosinophils. The mean fall in eosinophils from the control level was 48%. Almy et al. (1950) obtained similar data to ours in their study of adrenaline eosinopenia in two patients with neoplastic disease of the pituitary.

Unfortunately, quantitative histological data on the extent of viable pituitary tissue is not available in all these cases. Nevertheless the observation that significant eosinopenia developed in these patients after treatment with adrenaline or with ephedrine suggests that these drugs do not discharge A.C.T.H. by direct action on the pituitary, or via a neural link to the gland, but may increase the peripheral utilisation of cortical hormones, as proposed by Sayers (1950).

W. H. Robinson has informed us that he studied a patient with Addison's disease who was kept in good clinical condition by daily oral therapy with cortisone. When he injected adrenaline into his patient, there was a 70% decrease in the eosinophil-count. We tested two patients with Addison's disease, but their responses to A.C.T.H. and adrenaline were equivocal and may have been the result of chance, or of activity of viable remnants of adrenal tissue.

Accordingly we decided to study patients who had had both adrenal glands removed surgically. In the three patients with *surgical Addison's disease*, reported here, there was excellent evidence that the pituitary-adrenal axis was completely interrupted: the glands were completely removed surgically (proved macroscopically and microscopically by Dr. A. B. Ragins), and tests with potent A.C.T.H. provided no evidence of activity of accessory adrenal glands or rests. The accompanying table shows that there was very little change in the number of circulating eosinophils when either A.C.T.H. or the saline solution was injected. However, in each patient there was a significant decrease in the number of circulating eosinophils four hours after the injection of adrenaline. In cases 1 and 2 the decrease in numbers of the circulating eosinophils was 78% and 54% respectively. In case 3 there was only a 36% reduction of circulating eosinophils. However, his eosinophil-counts were abnormally high at the time of the study (2800 cells per c.mm.), and a decrease of more than 1000 eosinophils per c.mm. is highly significant under these conditions. The magnitude of response of the eosinophils to adrenaline in this patient corresponds to that of allergic persons and healthy persons with high eosinophil-counts when their normal adrenal glands are stimulated by single intramuscular injections of A.C.T.H. 40 mg. (Best et al. 1952).

THE EFFECT OF PARENTERAL THERAPY WITH ADRENALINE (0·3 MG.), A.C.T.H., OR SALINE SOLUTION ON THE NUMBER OF CIRCULATING EOSINOPHILS IN THREE PATIENTS WITH CARCINOMA OF THE PROSTATE TREATED BY BILATERAL COMPLETE ABLATION OF THE ADRENAL GLANDS AND MAINTAINED IN A EU-ADRENAL STATE WITH ORAL CORTISONE

Case no.	Age (yr.)	Diagnosis	Circulating eosinophils (cells per c.mm.) before and 4 hours after therapy with					
			Adrenaline		A.C.T.H.		Saline solution	
			0 hr.	4 hr.	0 hr.	4 hr.	0 hr.	4 hr.
1	62	Cancer of prostate with metastases; bilateral adrenalectomy	161	35	92	89	81	77
2	60	,,	41	19	28	39	31	25
3	47	,,	2848	1833	2301	2190	2733	2785

We interpret the above data to indicate that adrenaline eosinopenia does not necessarily develop as the end-result of successive stimulation of the hypothalamus, pituitary gland, and adrenal cortex, which is thought t be triggered by an injection of adrenaline, or by liberatio of adrenaline *from* the adrenal medulla. Adrenaline ca produce eosinopenia in the absence of either the pituitar gland or the adrenal but seems to require the presenc of adrenocortical hormones to be effective as an eosinopenic agent, since it is known that adrenaline does no produce eosinopenia in *untreated* Addison's diseas (Roche et al. 1950).

Studies made in our laboratories may shed som light on the combined effects of adrenaline an adrenocortical hormones on the eosinophil. Whe defibrinated human blood is incubated under steril conditions with cortisone or compound F, the eosinophi cells degenerate, and a significant eosinopenia develop (Muehrcke et al. 1952a). These changes do not take plac when saline solution, particulate matter, or other steroids such as deoxycortone and digitalis, are incubated wit defibrinated blood. When adrenaline was added to th mixture of cortisone and blood, the cortisone activit was not potentiated; and, when adrenaline was incubated by itself with defibrinated human blood, an eosinopeni did not develop (Muehrcke et al. 1952b). This suggest that the joint action of cortisone and adrenaline on the circulating eosinophils may be mediated through some organ, such as the lung, which is known to trap and destroy leucocytes (Bierman et al. 1951). Eosinophil-counts were made on arterial and venous blood sample taken during cardiac catheterisation. In a third of the patients the eosinophil-counts were much smaller in the arterial blood than in the venous blood, perhaps indicating trapping of eosinophils by the lung. Possibly in man adrenaline helps to sequester eosinophils in the lungs, and perhaps adrenocortical hormones act there to destroy them. This theory of trapping and destruction of circulating eosinophils *in situ* would explain why it is well-nigh impossible to find degenerated eosinophils in stained smears of blood taken from patients at the height of adrenocortical eosinopenia, even though 50% or more of the eosinophils have disappeared from the blood (Muehrcke, Lewis, and Kark, unpublished observations).

Our findings indicate that the four-hour eosinophil-response test to adrenaline should not be used to test the function or integrity of the pituitary-adrenal system in man. It remains possible that adrenaline stimulates the anterior pituitary gland of healthy people to liberate A.C.T.H. This could be tested by measuring the amount of A.C.T.H. or compound F (preferably the former) in the blood of healthy persons before and after an injection of adrenaline. So far as we are aware, such measurements have not been made.

SUMMARY

Three patients with carcinoma of the prostate had both their testes and adrenal glands removed and were maintained in a eu-adrenal state by therapy with oral cortisone. Direct eosinophil-counts were made before, and four hours after, the injection of adrenaline, saline solution, and A.C.T.H. There was a significant decrease in the number of circulating eosinophils after the injection of adrenaline, but A.C.T.H. and saline solution had no effect on the eosinophil level.

Thus, in the presence of cortisone, adrenaline eosinopenia can occur despite complete interruption of the pituitary-adrenal system.

For this and other reasons presented here the four-hour eosinophil response to adrenaline should not be used to test the function or integrity of the pituitary-adrenal system in man.

We wish to thank Dr. John G. Vandenberg for his kindness in allowing us to study his patients, and Mr. Tom Staples for helping us with the eosinophil-counts. This work was supported in part by a grant from Messrs. Armour, Chicago.

References at foot of next column

PSILATERAL REPRESENTATION IN THE CEREBRAL CORTEX

ITS SIGNIFICANCE IN RELATION TO MOTOR FUNCTION

P. GLEES
D.Bonn, M.A., D.Phil. Oxfd

J. COLE
B.Sc., M.A. Oxfd

From the Laboratory of Physiology, Oxford University

Gooddy and McKissock (1951), discussing the retention some function in the contralateral limbs after hemi- herectomy, point out that "residual function must pend on residual cerebral tissue." Like some earlier orkers, they suggest that "lower motor structures" ay a part in maintaining the patient's use of his limbs ntralateral to his lesion. To the assistance of these defined subcortical structures come normal cortical d subcortical structures from the intact hemisphere.

The results of our experiments on monkeys support is suggestion that the "uncrossed tracts" may in emergency be available to a patient.

Working on the recovery of motor function following all lesions in area 4 (Glees and Cole 1950), we found at neighbouring portions of the same motor cortex ke over the function of an ablated area. At the same me, our studies strengthened our assumption that the otor cortex can no longer be regarded as a mosaic- ke structure. Stimulation experiments by Liddell and hillips (1950) confirmed and amplified this view.

We also concluded that, though a particular subdivision g., the hand area) of the motor cortex sends most of its escending fibres to the appropriate segments of the rvical cord, a minority of fibres are connected with her levels as well. This is true for all subdivisions of ea 4. These plurisegmental connections of the sub- visions of the motor cortex within the cord offer an xplanation of motor recovery subsequent to small sions in area 4.

In this work we had developed quantitative tests for easuring the loss and recovery of power and dexterity the hand contralateral to the lesion (Cole 1952). hen we came to study ipsilateral impairment after sions in area 4, we were able by means of the same sts to state such impairment in quantitative terms. us we obtained evidence: (1) that cortical areas djacent to a lesion play a part in the recovery of function a contralateral limb, as was demonstrated by our rlier work; and (2) that fibres from the ipsilateral misphere participate in the motor activity of a limb. his latter finding suggests that ipsilateral fibres play important part in residual function in limbs after a mispherectomy.

We give below an outline of two cases in which our tests have indicated and measured impairment in the ipsilateral hand after experimental lesions in the motor cortex of monkeys.

Case 1.—A right-handed *Macaca mulatta* monkey, weighing 4·8 kg., was given multiple small lesions in the hand and face regions of area 4 of the right hemisphere. After operation there was gross paralysis of the left hand, while motor power, as measured by our test, had decreased in the right hand from 236 to 150 g. From this loss in the right hand recovery was made to the preoperative level within about a week, while gross impairment still existed in the left hand which later recovered. Dexterity also showed impairment and recovery in a similar manner to motor power.

Case 2.—A *Macaca nemestrina*, weighing 3·6 kg., taught to use both hands for the motor power test, received lesions in the left cortex, similar to those in case 1 but slightly more extensive. The hand contralateral to the lesion was not used for seven days but showed complete recovery of motor power in just under three weeks. The hand ipsilateral to the lesion showed a drop of 130 g. postoperatively, with recovery in a fortnight. The effect of this operation on both hands is shown in fig. 1. When recovery in both hands was complete, at a second operation lesions were made in the right cortex. This again demonstrated the importance of ipsilateral connections by causing fresh impairment in the right hand, shown by a drop in motor power of 46 g., which later showed recovery.

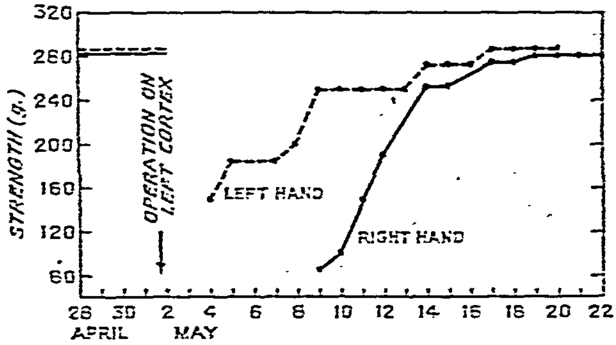


Fig. 1—Effect of multiple small lesions in area 4 in a monkey (case 2). The loss and recovery of motor power are illustrated for both hands.

Histological studies by the Marchi method were made in both cases, and in case 1 we counted the degenerated crossed and uncrossed fibres in the lateral corticospinal tracts at the various levels of the cord (fig. 2). Of the total number of degenerated fibres on both sides 15% were ipsilateral to the cortical lesion; this ratio is similar to what Glees et al. (1950) reported in a baboon after a small ablation in area 4.

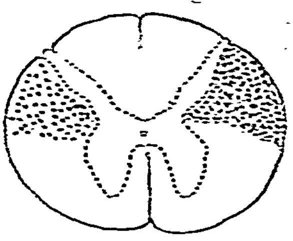


Fig. 2—Section of cervical cord illustrating crossed and uncrossed Marchi degeneration of the lateral corticospinal tracts (case 1).

These experimental findings are consonant with the statement that "residual function must depend on residual cerebral tissue" (Gooddy and McKissock 1951) and support their suggestion that, after hemispherectomy, ipsilateral fibres play a very large part in the considerable use that the patient retains in his limbs contralateral to his lesion.

Our view that this experimental evidence is relevant to man is confirmed by our histological study of a recent human case, which was made possible by the courtesy of Sir Hugh Cairns, Mr. W. S. Lewin, and Dr. P. Daniel, of the Radcliffe Infirmary, Oxford. This brain showed a complete pyramidal degeneration on the right side of the medulla, while the other side was normal. Apart from the crossed degeneration at spinal-cord levels on

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PROF. KARK, MR. MUEHRCKE: REFERENCES

elson, D., Moyes, E. N. (1950) *Lancet*, ii, 50.
lmy, T. P., Laragh, J. H., Cohen, E. J. (1950) *N.Y. Med.* 6, 16.
est, W. P., Muehrcke, R. C., Kark, R. M. (1951a) *J. clin. Invest.* 30, 629.
— — — (1951b) *J. Lab. clin. Med.* 38, 790.
— — — (1952) In the press.
— Samter, M. (1951) *Blood*, 6, 61.
— — Kark, R. M. (1950) *Proc. Inst. Med. Chicago*, 18, 189.
erman, H. R., Byron, R. L., Kelly, K. H., Petrakis, N. L. (1951) *Blood*, 6, 770.
annon, W. B., Rosenblueth, A. (1937) Autonomic Neuro-Effector Systems. New York.
Henneman, P. H., Wexler, H., Westenhaver, M. M. (1949) *J. Lab. clin. Med.* 34, 1017.
aller, J. W., Wong, A. S. H., Engle, E. T. (1951) *J. clin. Endocrinol.* 11, 188.
uehrcke, R. C., Lewis, J. L., Kark, R. M. (1952a) *Science*, 115, 377.
— — Peters, J., Kark, R. M. (1952b) Unpublished data.
Randolph, T. G. (1944) *J. Allergy*, 15, 9.
Recant, L., Hume, D. M., Forsham, P. H., Thorn, G. W. (1950) *J. clin. Endocrinol.* 10, 187.
Roche, M., Thorn, G. W., Hills, A. G. (1950) *New Engl. J. Med.* 242, 307.
Sayers, G. (1950) *In* Soskin, S. Progress in Clinical Endocrinology. New York; p. 182.
Selye, H. (1950) The Physiology and Pathology of Exposure to Stress. Montreal.
Smith, J. J. (1950) *In* Mote, J. R. Proceedings of the First Clinical A.C.T.H. Conference. Philadelphia; p. 161.
Solomon, D. H., Shock, N. W. (1950) *Ibid*, p. 44.
Wolfson, W. Q., Cohn, C. (1950) *Ibid*, p. 241.

the left side, a well-marked ipsilateral degeneration was found in the field of the right lateral corticospinal tract. This case shows that man also has a great number of ipsilateral fibres, as demonstrated in our Marchi preparations, descending in the lateral corticospinal tract.

REFERENCES

Cole, J. (1952) *J. comp. Physiol. Psychol.* (in the press).
Glees, P., Cole, J. (1950) *J. Neurophysiol.* 13, 137.
— — Liddell, E. G. T., Phillips, C. G. (1950) *Arch. Psychiat.* 185, 675.
Gooddy, W., McKissock, W. (1951) *Lancet*, i, 481.
Liddell, E. G. T., Phillips, C. G. (1950) *Brain*, 73, 125.

INSULIN-NEUTRALISING ACTIVITY OF GAMMA-GLOBULINS DERIVED FROM THE SERUM OF AN INSULIN-RESISTANT PATIENT

VITO DE FILIPPIS
M.D.

ANGELO IANNACCONE
M.D.

From the Institute of Medical Semeiology, University of Naples, Italy

THE development of insulin resistance has been reported in some cases as an immunity reaction (Lerman 1944, Lowell 1944a and b, 1947). Evidence of the presence of a neutralising factor in the serum of insulin-resistant patients was obtained by injecting mice with a mixture of serum and insulin and noting the absence or decrease of hormone effect.

The neutralising factor was supposed to be an antibody for insulin on the basis of the following data:

(1) When insulin is omitted, the resistance becomes less or disappears (Lowell 1944a and b).

(2) The capacity of antiserum to protect animals against the hypoglycæmic effects of insulin does not parallel the concentration of antibodies if the serum is diluted (Lowell 1947).

(3) The mixture was injected a few minutes after preparation. It is noteworthy that the glycotropic (anti-insulin) factor of the anterior lobe of the pituitary must be administered some hours before the insulin to be effective (Thomson 1942, Lowell 1947).

Our observations support the view that antibodies to insulin may be a cause of insulin resistance.

CASE-RECORD

A woman, aged 45, had had diabetes mellitus for six years. For last four years her insulin requirement fluctuated between 40 and 70 units. Insulin was withheld for about a year. In July, 1950, treatment was resumed because of weakness, loss of weight, and severe glycosuria. Increasing amounts of insulin were given in an attempt to control the diabetes, but 460 units did not clear the urine of sugar. Intravenous insulin, 10 units, produced a fall of about 14% in the blood-sugar level in two hours (the fasting blood-sugar level was 234 mg. per 100 ml.). Tests for endocrine glands and liver function showed no abnormalities. There was no other illness or infection and no manifestation of insulin allergy. Intracutaneous tests with crystalline insulin, the Prausnitz-Küstner reaction, and tests for serum precipitins were negative. Experiments to detect insulin-neutralising activity, made with the patient's serum, as suggested by Lowell (1944b), showed that the serum protected rats against the hypoglycæmic effects of insulin. The results indicated that the patient's serum contained an insulin-neutralising factor with some characteristics of an antibody (De Filippis and Iannaccone 1951).

Since much evidence indicates that antibodies consist of modified globulins and are usually, although not exclusively, associated with the gamma-globulins, it was expected that most of the insulin-neutralising antibody would be found in the patient's gamma-globulins.

INVESTIGATIONS

Material and Methods

Electrophoretic analysis of the patient's serum gave albumin 50%, alpha-globulins 9%, beta-globulins 17%, and gamma-globulins 24%.

Serum euglobulins were isolated according to th method of Kekwick (1940) and were found by electr phoretic analysis to consist of 96% [illegible]

12% and 4% solutions in 0·1 [illegible] containing 1 : 10,000 merthiolate as a preservative, wer prepared. To 2·5 ml. of each solution was added 0·5 m of crystalline insulin 40 units per ml. diluted 1 : 10(Albino rats, weighing 30–50 g. and starved for twenty four hours, were injected with *0·01 ml. of the mixtur* (containing about 0·008 ml. of gamma-globulins solutio and 0·00066 units of insulin) per g. body-weight. Th mixture of gamma-globulins and insulin was not incubate before testing. The rats were kept at a temperature o about 37°C and observed for two hours. Weakness o paralysis of the hind legs, loss of equilibrium, con vulsions, and coma were considered to be the effects o insulin. A quick recovery from hypoglycæmia followe intra-abdominal injection of a glucose solution.

Euglobulins of normal people, obtained by the sam method, were used as a control.

Results

22 rats were injected with the mixture containing 12% solution of normal human gamma-globulins: 20 of them showed evidence of insulin effect. 12 rats wer then injected with the mixture containing 12% solutio of gamma-globulins of our insulin-resistant patient: a hypoglycæmic reaction occurred in only 3 of them.

25 rats received a mixture containing 4% solution o gamma-globulins of normal people: 21 of them showed hypoglycæmic symptoms. 13 rats received a mixture containing 4% solution of gamma-globulins of our patient: *only 4 of them showed symptoms.*

RESULTS OF EXPERIMENTS ON RATS

Tests with gamma-globulins of normal people				Tests with gamma-globulins of insulin-resistant patient				
Gamma-globulins %	No. of rats tested	Hypo-glycæmia	No hypo-glycæmia	Gamma-globulins %	No. of rats tested	Hypo-glycæmia	No hypo-glycæmia	χ^{2}*
12	22	20	2	12	12	3	9	$\chi^2 = 12$ (n = 3; P < 0·01)
4	25	21	4	4	13	4	9	$\chi^2 = 8$ (n = 3; P < 0·05)

* With Yates's adjustment (Fisher 1948).

The accompanying table shows that the results are statistically significant.

Comment

Our findings indicate that gamma-globulins separated from the serum of an insulin-resistant patient protected rats against the hypoglycæmic effects of insulin.

We emphasise the fact that the insulin and gamma-globulins were mixed just before injection, and the mixture was used as soon as prepared and without incubating. Moreover dilution of gamma-globulins did not significantly reduce the anti-insulin effect; in fact the results obtained with a 4% solution were very like those obtained with a 12% solution.

This suggests that the neutralisation of insulin was due to an immunity reaction. Accordingly it seems justifiable to assume that anti-insulin antibodies were present in the patient's serum and were associated with, or consisted of, gamma-globulins.

SUMMARY

Gamma-globulins isolated from the serum of an insulin-resistant patient protected rats against the hypoglycæmic effect of insulin. This fact supports the view that insulin resistance may be due to antibodies for insulin.

We gratefully acknowledge the help of Prof. G. Tron, of the Istituto Sieroterapico Italiano, Naples.

References at foot of next column

New Inventions

OPERATING-SPECTACLES FOR AURAL SURGERY

THESE spectacles have been designed and constructed to fulfil a number of requirements found to be of practical mportance in certain aural operations which call for a moderate degree of magnification. Glasses of this kind have been in use for many years, and one variety, the Zeiss-Gullstrand, is particularly well known. In this, use is made of small Galilean-type telescopes carried in front of the eyes in metal spectacle frames with rather complex screw adjustments for interpupillary distance, convergence, &c. Such spectacles, however, are fragile and difficult to adjust and clean, and the rigidity of their attachment to the head falls far below that attainable with a well-fitted pair of spectacles. This seriously impairs their effective use as optical instruments. Moreover, it is necessary for the operator to remove them when operating on parts which do not need magnification, and for this reason they may need to be put on and taken off by an assistant several times in the course of an operation. This is time-consuming and may be very irritating, particularly when some manipulation is needed which calls for a prompt change to magnified vision.

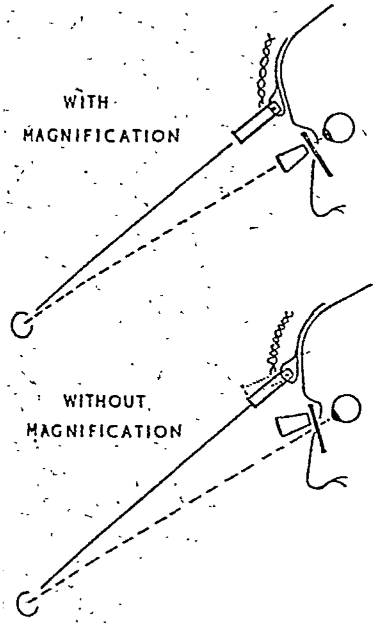

Fig. 1—Spectacles in use.

The operating-spectacles described here are designed to overcome these difficulties. They have as their basis a pair of accurately fitted spectacles carrying flat lenses which give any correction required for working at 10 inches. The Galilean telescopes are mounted upon a small light metal bar accurately constructed to provide the interpupillary distance and convergence to 10 inches needed by the individual user. The bar is carried upon two rigidly connected metal posts projecting forwards from the nasal portions of the lens frames. It is accurately sited upon these posts and rigidly fixed thereto with two small thumbscrews. The bar with the telescopes can be very speedily detached for cleaning and reaffixed with ease and precision.

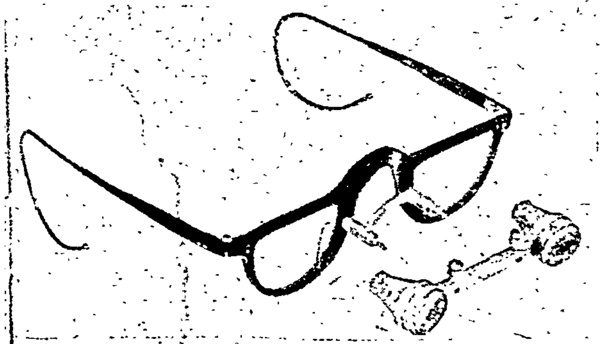

Fig. 2—Spectacles showing bar for carrying telescopes.

The size and conical form of the telescopes are such as to provide a minimum of obstruction to the visual field. By directing the gaze downwards by a matter of a few degrees a wide view of the unmagnified operation field is obtained through the spectacle lenses alone, without change of the working distance of 10 inches. This change of view necessitates, of course, a slight change in direction of the head-light which is usually worn. This can easily be achieved by the surgeon himself, who can thus, at any moment of the operation, switch to or from magnification without any delay or dependence on an assistant.

The optical quality of the telescopes is good; coated lenses are used, and light loss is thus minimised. Magnification is ×2 with a field diameter of $1^1/_4$ inches.

The spectacles are manufactured by Keeler Optical Products Ltd., 39, Wigmore St., London, W.1, who have solved several difficult problems of design and construction, in particular the fixation of the telescopes to the spectacle frame in a manner which combines comfort, rigidity, accurate positioning, and ease of removal for cleaning.

Otological Research Unit, Medical Research Council, National Hospital, Queen Square, and Aural Departments, National Hospital and University College Hospital, London

C. S. HALLPIKE
F.R.C.S., F.R.C.P.

Reviews of Books

Malignant Disease and its Treatment by Radium

Vol. 4. 2nd ed. Sir STANFORD CADE, F.R.C.S., surgeon, Westminster Hospital, London. Bristol: John Wright & Sons. 1952. Pp. 544. 63s.

THE fourth volume of this second edition has been almost entirely rewritten and becomes an up-to-date and authoritative description of the groups of tumour with which it deals. The first section describes the various types of cancer of the skin and of their treatment with radium. The illustrations are a reminder of the advanced lesions which are still sometimes seen, although now, with spread of knowledge and modern therapy, they are becoming rare. A photograph of a radium mould made of plastic material, such as are now in general use, might have been included. A chapter on malignant disease of the kidney, testis, and prostate follows and maintains the high standard. It is, however, in the chapters on bone sarcoma and on sarcomas of soft parts that Sir Stanford Cade's ability and experience are best shown. The amount of material available, the balanced outlook brought to the problems of treatment, and the detailed records of cases must all be helpful to those who have to make decisions about patients who are mostly young and whose disease calls for prompt action.

A new section on the pathology of tumours of lymphoid tissue has been added by Dr. George Lumb, who gives a clear classification which can be accepted, though with some reservation. The difficulty encountered is where to place Hodgkin's disease. Dr. Lumb recognises three separate types of lesion: (1) lymphoreticular lymphoma, of which he says "some of the cases which have been called early Hodgkin's and Hodgkin's-like probably belong to this group"; (2) Hodgkin's disease; (3) Hodgkin's sarcoma, which he regards as the anaplastic variety of the mixed-cell neoplasm of normal Hodgkin's type. The first and second types are sometimes found in the same patients, and so are the second and third, though admittedly some acute cases seem to be sarcomatous from the beginning. Surely all three are manifestations of the same condition, and a parallel is found in the reticulosis usually called Brill-Symmers disease, which also has three forms. It would also have been helpful had more emphasis been laid on the difficulty of differentiating the anaplastic sarcomas from certain anaplastic carcinomas—a point of great clinical importance.

The chapter on the leukæmias, by Prof. B. W. Windeyer and Dr. J. W. Stewart, gives a thoroughly competent account

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DR. DE FILIPPIS, DR. IANNACCONE: REFERENCES

De Filippis, V., Iannaccone, A. (1951) *Rif. med.* 65, 893.
Fisher, R. A. (1948) Statistical Methods for Research Workers. London.
Kekwick, R. A. (1940) *Biochem. J.* 34, 1248.
Lerman, J. (1944) *Amer. J. med. Sci.* 207, 354.
Lowell, F. C. (1944a) *J. clin. Invest.* 23, 225.
— (1944b) *Ibid*, p. 233.
— (1947) *Ibid*, 26, 57.
Thomson, D. L. (1942) *In* American Medical Association, Glandular Physiology and Therapy. Chicago; p. 56.

of the pathology of the many varieties, with good illustrations. Due weight is given to the different methods of treatment now available, and the great importance of maintaining the erythroblastic function of the marrow is recognised. There will be wide agreement that irradiation of the spleen is still the method of choice for the ordinary chronic case.

The last chapter, on intracranial tumours, includes sections on pathology by Dr. D. Williams, on surgery by Mr. Wylie McKissock, and on radiotherapy by Mr. J. Jackson Richmond. The satisfactory results recorded, together with some cases of long survival in patients treated with radium at the Westminster Hospital, show how much can be done for these tumours by a first-class team.

Now that the fourth volume of this textbook is available it becomes more than ever apparent that the whole is a work of great scope and interest. The first edition was outstanding, but the additions to the second have enhanced its merit. Nothing but praise can be found for the clinical descriptions, from which a student of cancer may build a sound knowledge of the disease. The knowledge, judgment, and enthusiasm which have gone to the production of four volumes, all on this high level, call for warm congratulations to the author and his collaborators.

Traitement des néphrites aiguës anuriques par les méthodes d'épuration extra-rénale

A. TZANCK; M. DEROT; J. J. BERNIER; M. BESSIS; J. DAUSSET; M. LEGRAIN; P. MILLIEZ; L. MOREAU; P. PIGNARD; P. TANRET. Paris: Masson. 1952. Pp. 176. Fr. 1200.

WE now recognise that anurias resulting from mismatched transfusion, septic abortion, and shocking injuries tend to spontaneous recovery in two or three weeks if the patient can be kept alive. The effort to maintain life during this critical period received a new impetus from Kolff's development of his artificial kidney. The French authors describe exsanguino-transfusion as the simplest way to avert progressive uræmia. Supporting methods are intestinal dialysis, peritoneal dialysis, or the driving of arterial blood through still another model of artificial kidney. The successful dietetic method of Bull, Joekes, and Lowe is described as a *solution draconienne.* The more sanguinary methods of the French authors are none the less successful and they obtained recovery in 58 out of 96 cases.

Despite its French bias, this book gives a reasonably good account of the literature. It contains a great deal of useful practical information on the specialised techniques involved.

Health Education

A guide to principles and practice. CYRIL BIBBY, M.A., M.SC., F.L.S. London: Heinemann. 1951. Pp. 222. 17s. 6d.

GRANDMOTHERS' tales die hard, and the general public is still ill informed on how to keep healthy. But would-be educators need to know what to teach, and how, and when. Mr. Bibby, who has had long experience in health education, shows excellent judgment and much common sense in the helpful book which he has written for teachers, parents, doctors and nurses. It is thoroughly readable and it will be easily understood by educated laymen and yet not bore those with technical or medical knowledge.

In his analysis of the methods and media of health education, Mr. Bibby describes five principles: the build-up of assumptions via environment; inculcating habits by training; imparting biological information; fostering attitudes to create a healthy outlook on life; and inspiring appreciations and ideals. He elaborates these through the different stages of development from the baby to the parent, and according to the type of educator. The appendix contains an ontogenetic scheme in tabular form, information on methods of introducing health teaching into the curriculum, on planning formal health education, and on the use of media, together with a list of films and filmstrips, a directory of health education organisations, and an annotated bibliography. Another section deals with health statistics, and Mr. Bibby rightly deprecates that mortality statistics have to be used in the absence of satisfactory information on morbidity; for they do not give a "picture of the degree of health and vigour of a community."

In considering personal health habits in relation to the attainment of a full and happy life, Mr. Bibby suggests that we should drop the idea of "keeping clean," and replace it by "getting clean on appropriate occasions." He regards the parent as the prime health educator, with teachers coming a close second. He treats school and college education in some detail, and he advocates special periods for health education. He also urges that the environment in schools and colleges should be up to the level of their health teaching.

Cardiac Pain

SEYMOUR H. RINZLER, M.D., F.A.C.P., adjunct in medicine and cardiovascular research unit, Beth Israel Hospital, New York. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952. Pp. 139. 27s. 6d.

THIS acceptable monograph from the American Lecture Series should interest the clinician. It contains a useful bibliography of 335 references, and covers in fair but well-chosen detail the history of the syndrome of angina pectoris, the anatomy of the nerve pathways of the heart, and the mechanism, differential diagnosis, and treatment, of cardiac pain. Of the 12 plates 10 are full-page sketches illustrating trigger-areas in chest muscles and techniques of local block therapy used in attempts to anæsthetise the somatic components of cardiac pain. Dr. Rinzler's own contributions to the subject have led him to give undue prominence to this method, but in other respects he has preserved a restrained balance.

Bacteria

K. A. BISSET, D.SC., lecturer in bacteriology, University of Birmingham; *assisted by* F. W. MOORE, B.SC. Edinburgh: E. & S. Livingstone. 1952. Pp. 122. 20s.

Dr. Bisset describes this book as a "natural history of bacteria." This it is not, since the attention given to bacteria in their native haunts is incidental. It is rather a system of bacteriology based essentially upon morphology. It applies to bacteria rules of determination and classification such as were devised by Linnaeus for larger plants. It is not the first venture in this line, but it is clear and dogmatic and it may profitably be read at least once by all who have a professional interest in bacteria. The medical bacteriologist, because like arises from like, wishes to label bacteria so that he may know them at a later meeting. To this end he uses his knowledge of their habits, natural and acquired, their antigenic make-up, and their biochemical parlour-tricks, in a practical but disorderly way, and he is content to label them with numbers or antigenic formulæ. To the systematist this appeals as little as the keeper at the Zoo who replaces the Linnaean system by such useful labels as "harmless," "dangerous," or "smelly."

Dr. Bisset's emphasis on morphology is in the classical tradition, but his line drawings are clearer than what is usually seen under the microscope. In his introduction he says "simplicity is characteristic of truth." He has in fact so simplified his account of the habits and properties of living bacteria that he has been forced back only too often on "rather" and "almost" in place of quantitative statement. We do not often ask for a larger book, but we hope that a second edition will be expanded in this direction, and, in view of the author's experience, an appendix on cytological methods would be valuable. It is interesting to see that there is no reference to work earlier than 1941.

The World of Learning (London: Europa Publications. 1952. Pp. 964. 80s.).—The fourth edition contains 83 more pages and costs 20s. more than the third edition did in 1950. As usual there is an index of institutions, but an "Index of Names" (presumably personal) is promised for separate publication in August, and it is intended that such an *index* will be included in future editions. Several countries have changed their places or [illegible] under new names: Salvador has mov[illegible] [illegible]rer the front as El Salvador; Iran has moved in the opposite direction as Persia; Eire has disappeared as such and reappears as Irish Republic; South Africa is now Union of South Africa; Netherlands Overseas Territories is split into Indonesia and Netherlands West Indies (which strangely consists of Curaçao and Dutch Guiana); and Saar is a newcomer.

THE LANCET

LONDON: SATURDAY, JUNE 14, 1952

Hospitals and the Public

In the old days very little publicity was given to e work of the municipal hospitals, but a great deal that of the voluntary hospitals, which depended gely on donations and legacies and therefore had to ep the public informed about their activities and eds. Under the National Health Service no group hospitals is financially obliged to cultivate good iblic relations, but it is none the less desirable that ery kind of hospital should do so. Local interest d good will is in fact one of those imponderable ctors that often make all the difference. Whatever e improvement in our remedies, the patient's nfidence will always play an important part in the ccess of treatment; and the reputation of the spital and its doctors, besides being therapeutic, may duce the delay before he seeks a consultation. od public relations also help to solve problems of affing, which are especially acute in industrial areas ere hospitals requiring manual and technical labour ve to compete with local factories working a five-y week. Again, in such an essentially humanitarian terprise, there remains much scope for voluntary fort, such as helping with the library, mending linen, siting the friendless, and organising entertainments. rtunately the Minister of Health has now ruled[1] at members of hospital authorities may take part the work of leagues of friends and similar voluntary oups, and that such groups may occasionally meet hospitals. Previously this was not allowed, with e result that such groups tended to lose touch with e needs of the institutions they seek to help.

Too often the service of a hospital is allowed seem less good than it really is; and it is well to member that local opinion may be influenced less the excellence of the medical care than by the urtesy of the gate porter, outpatient clerks, casualty rses, and telephonists, by the efficiency of the pointment system, and by the cheerfulness of the ain corridor. Attention to such matters should be assiduous as if the hospital were a hotel in competition with rivals; the impression ought to be given at it is a privilege for the hospital to receive the tient. One of the conclusions to be drawn from the udy of appointment systems, by Brigadier Welch d Mr. Bailey, which we lately published,[2] is that e smooth running of outpatient clinics depends on e consultant himself studying the details of organisaon, preferably with the records department. Can e really be satisfied with the kind of arrangements scribed in a letter on another page from a correondent who has been attending antenatal clinics? oreover, the kindly consideration extended to tients should also be extended to visitors; for ample, some accommodation for their children, hile they are visiting sick relatives, is much appreci-ed, as also are suitable arrangements for interviews with the doctors. Beyond this it is obvious that a first-rate service demands a contented hospital staff working under satisfactory conditions. Unfortunately the spirit of service so often evident under the voluntary system has been a little dimmed; and difficult conditions, once accepted uncomplainingly, are less well tolerated today, now that the concept of the "*bottomless national purse*" has replaced that of the publicised overdraft of the old days. A proper perspective and sense of responsibility will undoubtedly be encouraged by the joint consultative staff committees, which should have the support of the medical staff. This does not mean, however, that the medical side should surrender any responsibility borne by the medical advisory committee, whose statutory recognition is long overdue.

Of the other means of promoting public relations one of the most valuable is the help of the local press. Few advocate the attendance of the press at meetings of hospital committees, for this would sometimes lead to undue emphasis on transient difficulties, which if broadcast might be aggravated. The hospital committee, however, should encourage an informal press conference with the hospital secretary to keep the press aware of current developments, so that the public will be continuously interested in the hospital as a part of the local community. There is a good case likewise for having an annual view day, to which hospital staff can bring their relations and friends and at which an annual meeting can be held, attended by representatives of local organisations. There is much in a hospital which can be shown to the public, without embarrassment to the inpatients: the operating-theatre (not in use), the physiotherapy and reablement departments, the kitchens (would many have been allowed to become so archaic if they had been open to the public?), the pharmacy, the boiler-house (for the younger brothers), and the nurses' home (for the younger sisters). Such open days, which have proved useful in industry,[3] should in the long run have a valuable influence on recruitment of staff. They are already being held with success by some hospitals, and have been an established custom for many years at St. Bartholomew's, where, by tradition, the treasurer and "almoners" visit each ward to ask the patients whether they are comfortable and the consultant staff whether they are satisfied with the nursing. We are glad therefore to note that the Minister of Health[4] has lately reiterated his support of annual meetings open to the public, stating that the reasonable cost may be charged to the Exchequer. At such meetings printed annual reports could be distributed. The publication of such reports by management committees, which we urged some time ago,[5] was recommended last year by the Select Committee on Estimates[6]; and the Minister[4] has now agreed to this proposal, though we note with regret that the reports must be sold at cost price. They should provide in narrative form a general description of the group's activities throughout the year, including the main working statistics and salient figures in the accounts. Hitherto, hospitals have been forbidden to divulge their running expenses until the national summarised

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Circular R.H.B.(52)18; see *Lancet*, Feb. 2, 1952, p. 270.

Welch, J. D., Bailey, N. T. J. *Lancet*, May 31, 1952, p. 1105.

[3] *Industr. Welfare J.* July, 1951.

[4] Circular R.H.B.(52)33; see *Lancet*, May 31, 1952, p. 1120.

[5] Leading article. *Lancet*, 1950, i, 962.

[6] Eleventh Report from the Select Committee on Estimates. H.M. Stationery Office, 1951; see *Lancet*, 1951, ii, 573, 590.

accounts were presented to Parliament, by which time the local accounts were quite out of date; and we cordially welcome the ending of this embargo. Members of the hospital staff, in particular, should be regularly told about the cost of the service; for only thus will they keep in mind the need for reasonable economy and develop a sense of good housekeeping. Similarly, the medical activities of the hospital should be reported separately in a way designed to inform local practitioners.

With well-maintained public interest, hospitals could become important centres for instruction in preventive medicine, and especially in elementary dietetics and nutrition. There is still much scope for reducing the gap between the knowledge and the practice of simple health measures; and, in the continued absence of the hoped-for health centres, hospitals might become focal points for such teaching.

The Natural History of Disseminated Sclerosis

Though disseminated sclerosis is one of the commonest of organic neurological ailments, we are still largely ignorant not only of its cause but also of the factors affecting its course. Further, since there is no specific laboratory test for the disease, diagnosis depends wholly on clinical assessment. That this may be difficult is underlined by Kurland[1], who observes that in one large series of necropsy records the diagnosis had been wrong in about a third of the cases judged clinically to be disseminated sclerosis; while of those cases found post mortem a third had been unrecognised in life. Even when the diagnosis can be made with confidence, the prognosis for life and health is difficult to assess; for we know very little of the natural history of the disease. Now, however, valuable new information has come from two sources. McAlpine and Compston[2] have investigated the course of the disease in a series of 840 patients; while last month the *American Journal of Medicine* published a symposium on this and other demyelinating disorders.

McAlpine and Compston estimate that the prevalence-rate is about 1 : 2400 in England and Wales and 1 : 1570 in Scotland, with a slight excess of female over male patients. Of their 840 patients 35·3% were in their third decade at the time of onset, 20·3% were over forty, and 11% were between ten and twenty years old. Of 414 cases analysed in detail, 393 had episodic features in their course, with an average incidence of 0·39 attacks per year. The attack-rate did not vary significantly in relation to either the sex of the patient or the age at onset. With regard to remissions, some 35% of those having a second attack did so within one year, 54·5% within two years, and 75% within five years. In 5·3% of patients the first remission lasted for fifteen or more years, the longest remission being thirty-seven years; and of these patients with long remissions 68% had retrobulbar neuritis as the initial disturbance, compared with 32% for the group as a whole. Of the 414 cases, 43 were chronically progressive from the time of onset, and 103 entered this stage after preliminary remissions. Sex had no bearing on this aspect of the disease. McAlpine and Compston are, however, careful to point out that, as many of their patients were still in the early stages, their figures for chronic progression are probably an underestimate. On the basis of other studies—in particular those by Müller[3] and Allison[4]—they conclude that on average the patient survives for at least twenty years after the onset of the disease. Among writers recording particularly long periods of survival, Carter et al.[5] found, in a study of 46 cases proved at necropsy, 3 where the patients had survived for thirty-one to sixty-four years; and Denny-Brown[6] has personal case-records of 26 cases in patients over the age of fifty among whom the average duration of the disease was twenty-six years (11 had had it for over thirty years and 1 for fifty-eight years). Suggesting that the prognosis as to incapacity is on the whole better than is often inferred, Denny-Brown instances 2 patients of his own who reached the ages of seventy-nine and seventy-four after more than one bout of disseminated sclerosis between the ages of twenty and twenty-four; they were subsequently left with only mild disabilities, and 1 is still alive and getting about with the aid of a stick.

McAlpine and Compston discuss the factors affecting the onset and course of the disease in 250 patients, using as controls a similar number of hospital patients of the same age and sex distribution. Once more, as in an earlier study,[7] they found evidence suggesting that predisposition to disseminated sclerosis may be genetically determined; for 6% of their 250 cases were familial. They found no evidence, however, to support the claim[8] that, in addition to a specific tendency to develop the disease, a non-specific "more general neuropathic constitution" is inherited. They conclude that trauma (including dental extractions) and superficial infections may sometimes precipitate the onset of the disease and may, moreover, determine the site of the initial lesion. Anxiety and emotion, as Pratt[9] has previously indicated, may sometimes play a part; but like Müller[3] and Tillman[10] they found no evidence that pregnancy significantly affects the onset or subsequent progress of the disorder. Similarly nutritional factors are, in their view, of little importance. On the other hand, they found that a significant number gave a history of some allergic disturbance in the three months before the onset of the disease (8%, compared with 2·5% of the controls); while 11 relapses in 9 patients were preceded by allergic disturbances over a similar period. Again there was a significantly higher incidence of allergic disorders in the previous medical history of their patients than in the controls (27%, compared with 16·8%). Distinct temporary fluctuations in established symptoms (as opposed to true relapses) were induced, they found, by fever, anxiety, emotional disturbances, fatigue, external temperature changes, drugs, and blood-transfusions; and occasionally true relapses were brought on in the same way. Denny-Brown's[6] observations are relevant; for he suggests that the commonest cause of a relapse is lowering of general health and well-being, and he believes that patients who can lead a life of comparative ease are more likely to have long remissions. The geographical distribution of the disease varies distinctly; and a report by Canadian and Norwegian workers which has just reached this country provides a possible explanation. Swank et al.[11] find that in Norway the disease is more prevalent in farming than in other districts; and they suggest that a high intake of fat—and notably milk and other animal fats—may be among the precipitating factors.

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[1] Kurland, L. T. *Amer. J. Med.* 1952, 12, 561.

[3] Müller, R. *Acta med. scand.* 1949, suppl. 222.

[4] Allison, R. S. *Brain*, 1950, 73, 103.

[5] Carter, S., Sciarra, D., Merritt, H. H. *Proc. Ass. Res. nerv. ment. Dis.* 1950, 28, 471.

[6] Denny-Brown, D. *Amer. J. Med.* 1952, 12, 501.

[7] Pratt, R. T. C., Compston, N. D., McAlpine, D. *Brain*, 1951, 74, 191.

[8] Curtius, F. Multiple Sklerose und Erbanlage. Leipzig, 1933.

[9] Pratt, R. T. C. *J. Neurol. Neurosurg. Psychiat.* 1951, 14, 326.

McAlpine and Compston conclude that "the broad facts of the natural history of the disease are more compatible with the hypothesis of an allergic origin than with any other." They add, however, that in this study they are concerned only with possible exogenous factors; for as Lumsden[12] has suggested, in addition to a preparatory exogenous factor damaging myelin there may also be an endogenous mechanism related to the myelin sheaths or to oligodendroglia which liberates a myelinolytic substance. In the American symposium Hurst[13] says that the claim that the "hyperergic" histological changes found in disseminated sclerosis indicate an allergic origin is weakened by the demonstration that animals may become sensitised to products of breakdown of their own myelin. This does not mean, of course, that McAlpine and Compston are necessarily wrong. Other hypotheses are equally unproved: and Innes and Kurland[14] suggest that the possibility of a viral origin should be reinvestigated.

These observations have a twofold value. In the first place they provide a general background against which the prognosis in individual cases can be roughly assessed; and, secondly, which is more important, they underline the factors that tend to provoke a relapse. Still lacking, as we do, an effective remedy, we can probably best help patients with disseminated sclerosis by trying to prolong the remissions of the disease.

Carcinoma of the Pancreas

Although the removal of a carcinoma of the head of the pancreas or the ampulla of Vater is often undertaken, the results remain disappointing, chiefly because metastases are commonly present by the time laparotomy is performed. Better results must depend on earlier diagnosis, and in an attempt to discover how this may be achieved Brown et al.,[15] of Boston, have analysed the histories of 100 patients in five hospitals where the diagnosis of carcinoma of the pancreas was confirmed at necropsy. The sex-distribution agreed with that found in other series, 75 of the patients being men; and 51 were over seventy years of age. The commonest initial symptom was pain, which preceded the others in 52 cases; but in only 5 of these did it fit the usual description—severe, deeply seated in the epigastrium, and radiating to the back. Its most distinctive feature was its persistence, but it was often mild in degree and variable in position. While 30 patients had epigastric pain, in 44 the pain was situated elsewhere in the abdomen, in the back, or in the chest. It has been said that carcinoma of the body or tail of the pancreas is likely to give pain in the left side of the abdomen, but Brown and his colleagues found only 4 patients with such a pain, and in 2 of these the carcinoma was in the head of the pancreas. Jaundice appeared at some time in the course of the disease in 58 cases, and it was painless in 16. Loss of weight was a common and characteristic symptom, and as it often preceded any digestive disturbance it could hardly have been due primarily to impaired absorption of food. It is noteworthy that 26 patients had fever, and that leucocytosis was also a comparatively frequent finding, being present in 40 out of 69 cases in which a blood-count was made. Arkin and Weisberg[16] also found a leucocytosis in more than half of a series of patients with carcinoma of the pancreas, and they noted that it was usually associated with metastases.

Brown et al. point out that one of the most important indications of pancreatic disease is to be found in the stools, which had not been examined in many of the cases that they analysed. The stools of patients with pancreatic insufficiency are very bulky, and their weight when dried is much greater than normal. They may also contain visible fat, especially when the fat-content of the diet is high. As early as 1833 Richard Bright[17] described 3 patients whose stools contained yellowish fatty matter, resembling butter which had melted and then become solid again. In all 3 a carcinoma of the pancreas was found post mortem. The presence of visible fat is of much greater diagnostic significance than an excess of microscopic fat, which may also occur in other forms of obstructive jaundice and in sprue. The statement is current that when fat is found on microscopical examination to be chiefly in the neutral form, pancreatic insufficiency is the cause; but this is not always correct, for in the total absence of pancreatic enzymes there is sometimes no increase in neutral fat, which can be split by bacterial and other enzymes. Another well-known but seldom sought abnormality of the stools in pancreatic insufficiency is the presence of undigested muscle-fibres, found on microscopical examination. Muscle-fibres are most likely to be seen if the patient is given at least 100 g. of finely chopped beef or ham daily for three days; a carmine marker can be given at the same time as the meat. Further information from the stools can be obtained by quantitative estimation of the fat and nitrogen content of the dried stools while the patient is on a standard test-diet.

Occult blood, which was present in 67 of the 100 cases, is of little help in the differential diagnosis, and is indeed likely to give rise to the mistaken diagnosis of some gastro-intestinal lesion. The blood-diastase level was raised in 7 of the 17 cases in which it was estimated, and this test might be more widely employed. The secretin test, in which samples of pancreatic juice obtained by duodenal aspiration are examined, was positive in the 2 cases in which it was performed, and positive results have been reported by other workers in a high proportion of cases of pancreatic disease. X-ray examination of the gastro-intestinal tract was made in 36 cases, and in 10 it provided evidence suggesting pancreatic disease;

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[11] Swank, R. L., Lerstad, O., Strom, A., Backer, J. *New Engl. J. Med.* 1952, 246, 721.

[12] Lumsden, C. E. *Brit. med. J.* 1951, i, 1035.

[13] Hurst, E. W. *Amer. J. Med.* 1952, 12, 547.

[14] Innes, J. R. M., Kurland, L. T. *Ibid*, p. 561.

[15] Brown, R. K., Moseley, V., Pratt, T. D., Pratt, J. H. *Amer. J. med. Sci.* 1952, 223, 349.

[16] Arkin, A., Weisberg, G. *Gastroenterol.* 1949, 13, 118.

[17] Bright, R. *Med. Chir. Trans.* 1833, 18, 1.

but BROWN et al. consider that radiography is less valuable in diagnosis than the examination of the stools, the blood-diastase, and the secretin test. INNERFIELD and ANGRIST[18] found that, in pancreatic carcinoma with jaundice, estimation of the antithrombin titre may help in early diagnosis. In 11 patients who had been jaundiced for less than a month, the antithrombin titre was raised, and at laparotomy all the growths were found to be operable. In more advanced cases the antithrombin level fell to normal or below; a low figure was especially associated with involvement of the liver. Normal antithrombin levels were obtained in 109 out of 113 patients with obstructive jaundice due to acute biliary-tract disease.

Early diagnosis of pancreatic carcinoma must depend ultimately on early laparotomy. But if some of these tests for pancreatic insufficiency, particularly the examination of the stools, were regularly performed when a patient in the cancer age-group develops abdominal pain and begins to lose weight, with or without jaundice and with no clear evidence of gastro-intestinal disease, then laparotomy might be undertaken in more cases before the growth becomes inoperable.

Annotations

COLLOIDS AND CALCULI

WHY are Negroes less prone to urinary calculi than white people? The difference may be explained, in part at least, by the fact that Negroes have more colloids in their urine. These protective colloids enable both electrolytes and non-electrolytes to remain in solution in the urine in much higher concentrations than their solubilities in pure water would allow. Attracted by the possibility that stones may form when this protection fails, Butt and Hauser[19] have measured—by surface-tension experiments, by counting the particles visible microscopically, and by other means—the hydrophilic colloids in the urine of several hundred people of various races, including a number living in West Florida, where urinary calculi are common. They found that those with the least concentration of colloids in their urine were the ones who developed stones most readily. Women generally had more colloids than men, and the difference was increased during pregnancy. Stasis and infection are often said to be predominant causes of stone; but, quite apart from pregnancy, urinary infection is commoner in women, suggesting that they should have a greater tendency to stone formation than men. That the reverse is so supports Butt and Hauser's conclusion that colloid depletion is the main factor in the disease.

For a long time an imbalance between crystalloids and colloids has been thought to be a contributory cause, but no precise details of the mechanism are known, and certainly the idea has found little application in the prevention or treatment of calculi. Indeed attempts to stop stones forming have not on the whole been very successful. Butt and Hauser thought that hyaluronidase, the "spreading factor," might increase the protection given by urinary colloids in people who develop stones quickly. This enzyme encourages the natural colloids to form a gel which entangles the crystal nuclei as they appear and stops them from agglomerating and growing. They found, for example, that the low-colloid urine of a man who had been troubled by recurrent stones normally produced several large crystals and many smaller ones when allowed to evaporate on a microscope slide; but after an injection of hyaluronidase the tiny crystals were seen to be dispersed in a mass of gel, which is what happened when urine of normal colloid content was evaporated. Twenty patients in whom stones had been common were treated in this way, and eighteen have been free from trouble for from 11 to 15 months. Clearly this is not enough to justify definite claims of success, nor do the authors make such claims, but their ingenious method promises well, and we hope that a larger series of cases is in preparation.

PROVISION FOR THE MENTALLY DEFECTIVE

SOME mentally defective people, like some of the rest of us, are pleasant to live with; others are not. But all mental defectives above the grade of idiot, however they may turn out later, need special training in childhood to help them to fit into a world which is always going to be beyond them; and some, of course, will need to live in institutions, apart from the general community, for life.

In the *Times* of April 7, Lady Norman and Prof. D. R. MacCalman *said that of the 100,000 mentally defective* people in the country, only 57,000 have found places in institutions; and of those who have not, 12,000 are children who need education in special schools. Much hardship lies behind this bald statement, as a recent study[1] by the Socialist Medical Association in Sheffield illustrates. The committee which made the study mentions the case of a family where a man earning a good wage applied to a charitable society for financial help because one of his four children was a mental defective so destructive of bedding, crockery, clothing, and furniture that the father could not provide adequately for the rest of the family. Another mentally defective boy of eighteen, who lived with his mother, was not only destructive but dangerously violent; he was finally admitted to an infirmary intended for the elderly and chronic sick. At the other end of the scale are to be *found charming and amenable mentally defective children* who could profit greatly by special education and never got it. In Sheffield (which no doubt reflects the state of things elsewhere) there are some 4000 defectives of all ages. In the day special schools there are 360 places instead of the 720 estimated to be needed. These *schools* not only give the children the chance to develop their limited powers to the full but also greatly diminish the risk of the high-grade defective falling into delinquency.

> In Sheffield, besides special schools, there are three special classes in ordinary schools, receiving about 60 dull and backward children who are not sufficiently retarded to need educating in special schools. Occupation centres have proved successful for imbecile children found to be ineducable; here the emphasis is on character and habit training, simple handicrafts, coördination, and *simple domestic tasks*; and senior occupation centres run on the lines of sheltered workshops take boys over sixteen and endeavour to train them for employment in industry—sometimes very successfully. *There is only one* occupation centre for Sheffield; Leeds, with a smaller population, has four centres. In scattered areas the local authorities have power to arrange for simple instruction of the child in his own home; but the amount of training given is limited by the amount of staff available. In Sheffield 6 mentally defective children were taught at home in 1950.

Difficult, delinquent, or unmanageable mentally defective children often do best in a residential school, and training in such a school may keep them from qualifying for borstal or, eventually, for a term of imprisonment. Psychiatrists often report to a juvenile court that in order to prevent further delinquency a child or young person should be sent to a residential special school; but there are no such schools in Sheffield, or in many other places. The committee found that 9 Sheffield children were being sent to residential schools in other parts of the country, but the number estimated to need such care was 148.

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[18] Innerfield, I., Angrist, A. *Amer. J. med. Sci.* 1952, 223, 422.
[19] Butt, A. J., Hauser, E. A. *Science*, 1952, 115, 308; *New Engl. J. Med.* 1952, 246, 604.

[1] The Mentally Defective. Prepared by the Sheffield branch of the Socialist Medical Association and obtainable from Dr. C. H. Foggitt, 754, Attercliffe Road, Sheffield, 9. *Pp.* 10. *1s.*

Low-grade defectives, like the eighteen-year-old boy described above, need to live in a mental-defective colony or institution: they are quite unfit to be managed by their family. Here again we are intolerably short of accommodation. In October, 1951, there were 826 defectives in Sheffield urgently needing admission to such institutions—and a ten-year waiting-list. Some of these defectives are now serving prison sentences. Defectives who become destitute or unmanageable are sometimes admitted to inappropriate surroundings: 200 are in a Sheffield mental hospital occupying beds needed badly by the mentally sick, 115 are in an infirmary, some of them sharing the same quarters as sane epileptics and mentally sick people.

There is another side of the institutional picture. A child who has grown up to be a friendly and useful resident may not willingly be relinquished in favour of a difficult and unruly newcomer. The committee is not alone in finding " some undue reluctance on the part of those in charge of mental defectives in institutions to recommend patients to be placed on licence." The proportion of those on licence varied in different areas, suggesting a personal element in the decisions: thus in the Sheffield hospital region the proportion of those in institutions to those released on licence was 10 : 1; in Sheffield itself it was 6 : 1.

> The committee quotes the case of a boy sent into a colony at fifteen and later transferred to an institution until he was thirty-one; then by some mistake his detention order was not renewed. He went into lodgings, attended a Government reablement unit for twelve weeks, and found himself a job, in which he is now earning £9 a week.

This case is striking, of course, but not without parallel. Of 113 mental defectives on the disabled persons' register in one county borough in 1951, only 6 were unemployed at the end of the year. The committee suggests that if evening classes in the three Rs were arranged for high-grade defectives in institutions, the number registered for employment might be much greater. As it is, some high-grade defectives are quite equal to semi-skilled work like driving a crane.

Like the rest of us, the committee wants more accommodation for low-grade, difficult, and helpless patients, more occupation centres, special schools, and social clubs, and more research. They also urge the need for homes where low-grade children can stay for a short time so that their mothers can get a rest. A Ministry of Health circular (no. 5/52) not long ago impressed on local authorities their power to provide short-term care for mental defectives in cases of urgency. Authorities are free to find accommodation and pay for all or part of the maintenance of the defective for a period usually not exceeding two months. The Board of Control have also agreed that, in cases of emergency, superintendents of mental-deficiency institutions may take in defectives for short periods without legal formalities.

All these suggestions made by the S.M.A. committee are sound, but they bring us face to face with the difficulty of providing buildings and staff. Buildings perhaps are less difficult to find than staff: there are still a few large houses available for reconditioning. Staff is a more difficult problem, for those who have not worked with mental defectives have only heard, as a rule, about the unruly and difficult ones and have never realised how pleasant, kindly, and affectionate most of them are. The National Association for Mental Health has lately published a memorandum on the training and functions of nursing and teaching staffs of mental-deficiency hospitals in which they emphasise that senior nursing posts should be held by nurses fully trained in mental deficiency. To attract nurses to this work—which many find, once they have tried it, both congenial and rewarding—they have published a little pamphlet, " A Career for You ? " [2] which shows in photographs something of the patients and their life, and of the amenities which the nurse in a mental-deficiency institution may nowadays expect.

These are useful approaches to the subject; but it needs much more general attention than it is getting at present. Special schools, classes, and occupation centres are the most urgent need; for they cater for the higher-grade defectives and give them a chance of adapting themselves so well socially that they never need other institutional care at all. In the *Times* of April 16, the general secretary of the National Council for Civil Liberties, like the S.M.A. committee, urged " a more courageous policy in respect of the release of high-grade patients " from institutions. There are difficulties in applying such a policy, not merely because the work of the best patients makes it possible to run the institutions economically but because life in the outside world is a severe test of the stability of released patients. We need more halfway institutions to serve as training and testing centres, like the agricultural hostels which, for mentally defective labourers, have already proved their worth.

TALKING OF RADIOGRAPHS

WHEN describing radiographs of the chest, radiologists, physicians, and surgeons use certain terms—such as mottling, infiltration, and fibrosis—whose meaning may be precise enough in their own minds, but which may convey quite a different picture to others. In an effort to avoid such misunderstandings, the Joint Tuberculosis Council, the Faculty of Radiologists, and the Society of Thoracic Surgeons appointed a committee to consider the standardisation of radiological terminology in pulmonary disease, and the committee has now issued a valuable report.[3]

It is not enough, the committee says, for members of one specialty—radiologists, for example—to understand what other radiologists mean by a particular word or phrase; its meaning must be equally clear to all those concerned with the treatment of chest diseases—physicians, surgeons, and general practitioners. Of the radiologist's written report, the committee think: " In general it should be the standard practice for the report to be primarily descriptive, with the radiologist's interpretation added." A number of terms, both descriptive and interpretative, are then defined, and some limitations to their use suggested. " Fibrosis," for example, is thought to be permissible only when there is conclusive evidence of traction on other structures—e.g., the diaphragm, hilum, trachea, or intrapulmonary vessels. " Infiltration," commonly reserved for tuberculous lesions, may be just as apt in carcinomatosis, lymphadenoma, pulmonary suppuration, and other conditions. The word should only be used in a report when it is clearly understood to be interpretative, and when an opinion on the probable cause is also given. The committee emphasises that words referring to the activity of a disease are justified only when a series of radiographs is available for comparison.

The names " field," " zone," " apex," and " base " often mean different things in different countries, and the committee now gives them precise definitions. The general adoption is urged of the nomenclature approved by the Thoracic Society for the main bronchi and the pulmonary segments,[4] and this system is set out and illustrated.

The committee was also asked to bring up to date the report on Standards of Technique in Chest Radiography adopted by the Joint Tuberculosis Council in

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[2] Copies of the memorandum and of this pamphlet may be had from the National Association for Mental Health, 39, Queen Anne Street, W.1.

[3] Ministry of Heal [illegible] in Pulmonary [illegible] Radiography.

[4] *Thorax*, 1950, 5, 222.

1948. Slight variations in technique may lead to misinterpretation, especially when judging progress by comparison with previous films, and the routine suggested in the revised report will be examined with interest by all radiologists. It has been assumed that before long most chest radiographs will be taken by X-ray tubes capable of carrying at least 400 milliamperes. When the maximum available output is less, it is better to reduce the tube-film distance rather than increase the exposure time. The photo-electric timer, which automatically ends the exposure after a time appropriate to the size of the patient, is mentioned as a means of achieving more uniform radiographs. Those who have had the opportunity to examine a series of radiographs of the same patient taken by different radiographers with the aid of the phototimer will appreciate its value. Details of processing are included to re-emphasise the importance of great care in the darkroom.

ACUTE RENAL FAILURE

ACUTE renal failure has been the subject of much debate in the past decade. There are several distinct types, which can be identified by the clinical history and pathologically. Once anuria has developed, however, the clinical course and the treatment are similar in all types. This similarity has led many workers to postulate for every type of acute renal failure a " unity of pathogenesis "—a unity either of the initiating disturbance in the kidney or of the morphological lesions which develop there, or of the functional disturbance which results from these lesions. The number of these unifying hypotheses is increasing. Some of the clearly defined explanations appear to apply to one type of renal failure but not to others. By contrast, other explanations apply to all types but are so vague that they have little significance.

A refreshing paper on the pathogenesis of acute renal failure comes from Oliver et al.[1] who have made a careful study of the kidney by microdissection—a very old technique which has been perfected and used with great success by Oliver in the investigation of other renal conditions. These workers distinguish two kinds of lesion involving the renal tubules, and offer an ætiological explanation for each. The less common lesion is necrosis of tubular epithelium, confined to the proximal convoluted tubules and distributed evenly among all the nephrons. This necrosis is caused directly by tubular toxins which affect a specific part of the proximal tubule. The toxin is believed to act chemically on the epithelium; but experimentally Schlegel's technique revealed that it also greatly disturbed the blood-supply to the renal cortex.

The second lesion, described as tubulorrhexis, was present in all clinical cases of acute renal failure. This lesion was originally identified histologically in the crush kidney by Dunn et al.,[2] and was recorded by Darmady[3] who used the microdissection technique. Oliver's account is more detailed and more fully documented than the earlier descriptions. The change consists in localised necrosis of tubular epithelium associated with disintegration of the basement membrane at the same point, so that the tubule is disrupted. The lesion occurs principally in the distal convoluted tubules or the collecting tubules, but is common also in the spiral segment. It can sometimes be found in other parts of the proximal convoluted tubule or in the loops of Henle, but is difficult to identify at these sites. It is always very irregular in its distribution among different nephrons; and Oliver and his colleagues interpret this irregularity as indicating that the tubulorrhexis must be produced by patchy ischæmia. This interpretation is, however, open to doubt. In man the kidneys did not show any of the other lesions which are accepted as characteristic stigmata of severe ischæmia. Furthermore, in dogs pure renal ischæmia produced necrosis of proximal convoluted tubules but not localised tubulorrhexis. Oliver thus suggests that exactly the right degree of ischæmia must be applied to produce tubulorrhexis. It is difficult to accept that so delicately balanced a mechanism can account for a lesion found so very commonly in the kidneys of patients with anuria.

The common type of tubulorrhexis affects the " lower nephron " and is invariably associated with casts in these segments. It can be reproduced experimentally in dogs with renal ischæmia followed by intravenous injection of hæmoglobin, which produces casts in the lower segments of the nephron. The casts are often above or below the site of the tubulorrhexis, rather than at it; and Oliver believes that they do not cause the lesion. It must, however, be pointed out that in most of the clinical cases the patient had survived for nine to twelve days after the original damage to the kidney; and thus the condition of the affected tubule at the time of this damage can only be inferred. Secondly, those unversed in the technique will inevitably ask whether casts might not be moved along the tubule in the course of the dissection and disentangling of the individual nephrons with needles after the kidney has been macerated in concentrated hydrochloric acid for twelve to twenty-four hours. The possibility therefore remains that the tubulorrhexis in the lower segments of the tubule may be a mechanical effect of casts in the lumen.

Other problems are raised by this work. Oliver interprets the monocytic infiltration of the intermediate zone as a local reaction to tubulorrhexis of the spiral segments rather than as an indication of tubular leakage in the medulla. He maintains that tubulorrhectic lesions can heal only with great difficulty, either by the adhesion of connective-tissue fibres or by the irruption of granulation tissue. He believes that tubulorrhexis is important because the urine from the affected tubule escapes into the interstitial tissue or neighbouring vessels, instead of being excreted. Furthermore, it is suggested that the leakage of albuminous urine into the interstitial tissue produces œdema there, which impedes the flow of urine down the tubules of the region and compresses the capillaries, producing further ischæmia.

These ideas are all debatable, and there is no doubt that they will be widely discussed.

DIGITALIS AND VENOUS PRESSURE

EXACTLY how digitalis works is still uncertain—though not for want of trying. It seems definitely to increase the contractile power of the heart, and, as Cushny[1] showed over a quarter of a century ago, it causes arteriolar constriction. There is also a good deal of evidence that in normal animals its administration is followed by diminished cardiac output; but the reason for this is still disputed. Dock and Tainter[2] suggested that the explanation lay in a constricting action on the hepatic veins which reduced the venous return to the heart; but subsequent investigations have not consistently confirmed this observation.

Tyrer[3] has approached the problem afresh in a study of sheep in which the heart was replaced by a double-perfusion pump, thus excluding cardiac action on venous pressure. In four such sheep the addition of digoxin to the systemic venous reservoir was followed by a rise of pressure in the inferior vena cava. Since pulmonary and systemic circulations were perfused at a constant rate, total blood-flow through the venæ cavæ into the systemic venous reservoir was constant, and the central venous pressure was fixed at zero. Tyrer suggests that the rise of venous pressure evoked by digoxin can be explained in three ways: (1) " a slight general venoconstriction along the length of the inferior vena cava, increasing slightly the gradient of pres [illegible] ation of the

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1. Oliver, J., MacDowell, M., Tracy, A. *J. clin. Invest.* 1951, 30, 1305.
2. Dunn, J. S., Gillespie, M., Niven, J. S. F. *Lancet*, 1941, ii, 549.
3. Darmady, E. M. *Brit. med. J.* 1950, ii, 349.

1. Cushny, A. R. [illegible]
2. Dock, W., Taint[illegible]
3. Tyrer, J. H. [illegible]

venous system from the periphery"; (2) a localised sphincter-like venoconstriction of the upper part of the inferior vena cava; or (3) a selective action by the digoxin, causing a diminished blood-flow along the superior vena cava and an increased blood-flow along the inferior vena cava. Tyrer regards this third possibility as unlikely; and he concludes that the evidence of a peripheral action of digoxin on venous pressure is unequivocal. On the other hand, this "is not to suggest that the principal action of digoxin in intact sheep is on venous pressure." Indeed Tyrer describes experiments in four control sheep with intact circulations in which the intravenous injection of digoxin caused either no alteration or a slight fall of mean right atrial pressure.

This fresh evidence from Australia strongly supports the hypothesis that digitalis has a primary action on venous pressure, and it will be interesting to see whether other investigators can confirm these observations.

PERCUSSION

Leopold Auenbrugger (1722–1809), the son of an Austrian innkeeper, and in his youth a picturesque tapper of wine-barrels, later gained eminence as a physician by his ability to apply his powers of careful observation and percussion; but his *Inventum Novum* (1761), like many good discoveries, lay unnoticed for fifty years until Napoleon's physician, Courvoisart, translated it into French. Though some now regard percussion lightly, others hold it so useful that they practise it not only on the chest but also on the head, abdomen, and joints; and at least one eminent teacher draws attention to the "dull sound of an absent knee-jerk." There is no doubt that, as a means of comparing the resilience of one part of the body-surface with another, percussion is a valuable art.

One of the difficulties with percussion is in trying to remember the absolute quality of a sound; and the most successful exponents limit their observations to a comparison of sounds from adjacent points, or from corresponding points on the two sides of the body. Burger et al.[1] have gone some way towards defining how percussion is done; but what factors determine the quality of a percussion-note, and why do the underlying structures of the body influence the character of a sound radiated when the surface is struck? The sound that reaches the ear is radiated from the body-surface; each minute area of surface disturbs the air in its immediate neighbourhood, and the disturbance is transmitted to the ear with the velocity of sound in air. The ear summates the multitude of small components into a whole "sound," movements of air particles in one direction cancelling out those that arrive at the ear simultaneously with an opposite movement. Thus the two sides of a vibrating sheet produce opposite effects, and if the distance to the ear from opposite sides is the same no sound is heard however violently the sheet is shaken. One has only to percuss one's finger lightly in space, or shake a small fragment of paper, to demonstrate this. For this reason loudspeakers need a baffle. Every sound can be regarded as the sum of a number of pure tones. The note middle C has a frequency of 256 cycles per second, and in the time of one complete oscillation sound travels about 50 inches. Thus for this frequency of vibration to cause a maximum sound, the vibrating surface must be of such a size that the sound-path difference from the two surfaces to the ear is about 25 inches. Some sound will be heard, however, if the path-difference is less—say, greater than 5 inches. High notes are readily radiated from small surfaces, but low notes require a large vibrating surface or baffle area.

When a well-ventilated part of the chest is percussed a large area of the surface is momentarily depressed and vibrates as a whole; a relatively low note is produced and dies away at a speed depending on the viscosity of the skin and adjacent structures, of which the pleximeter finger is a small part. When fluid or a structure such as the liver underlies the surface, the part, although equally elastic, is less compressible. The surface is not depressed as a whole; but the part under the struck finger is depressed while the surrounding tissue rises at the sides of the finger and a wave spreads over the surface with the velocity of sound in tissue, just as a pond surface is disturbed by a falling stone. Such a surface gives a higher-pitched sound, and the more complex wave pattern gives rise to a higher rate of damping, with the characteristic dull sound. Echoes from internal surfaces or cavities are sometimes said to contribute to the quality of the sound. Possibly a large air cavity near the surface may resonate and produce surface ripples; and this may account for the high-pitched, undamped, resonant quality known as tympanic which is elicited over an empty stomach or a pneumothorax.

Sound echoes of frequencies beyond the range of hearing—e.g., 2 megacycles per second—can be elicited from internal body structures, in the same way as the ocean bed is depth-sounded by sound pulses from piezo-electric or magneto-striction radiators. The echoes are amplified and presented on a radar-type cathode-ray screen. Flaws in machinery and other industrial products are commonly located in this way; and work now proceeding in this country shows that in the body gross changes in internal density or elasticity can be detected similarly, though the waves do not go beyond an air interface. Such a procedure will determine the thickness of tissue overlying bone, show some defects in bones, and enable some structures, such as the liver and heart and pleural effusions, to be outlined.

THE BIRTHDAY HONOURS

Those who value tradition in such matters will be happy to see that a baronetcy has been conferred on Sir Cecil Wakeley, as on so many of his forerunners in the presidency of the Royal College of Surgeons. Since his first election in July, 1949, Sir Cecil has both exemplified and reinforced the vitality of his college, and the honour he has so well deserved will give all the more pleasure because Lady Wakeley and his son are also members of our profession. Mr. Walter Elliot, who must have been disclaiming other titles since the '20s, becomes a Companion of Honour, a designation earned alike by his public work and personal distinction. As is similarly appropriate, Lieut-General Sir Neil Cantlie is promoted K.C.B. in recognition of his notable work as director-general of medical services. The knighthood for Prof. W. E. Hume sets the seal on a valuable and distinguished career which included service in France as a consulting physician to the Army in the first world war, the chair of medicine at Newcastle, and the offices of senior censor and Harveian orator in the Royal College of Physicians. Group-Captain H. R. G. Poate, who is also created a knight, was president of the Royal Australasian College of Surgeons from 1945 to 1947, and Dr. Edgar Laurent is a member of the Executive and Legislative Councils of Mauritius. The names of other doctors appearing in the Birthday Honours are set out on p. 1205, and they form an impressive group. Outside the confines of medicine we are glad to note that Mr. J. M. K. Hawton, secretary to the Ministry of Health, is created K.C.B., in somewhat tardy recognition of his important contribution to the planning of the health service. Prof. R. A. Fisher, F.R.S., the eminent geneticist and statistician, and Mr. B. H. C. Matthews, F.R.S., the new professor of physiology at Cambridge, are among the new knights, and Miss Mabel Liddiard, retiring president of the Royal College of Midwives, is appointed C.B.E.

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[1] Burger, H. C., Casteleyn, G., Jordan, F. L. J. *Acta med. scand.* 1952, 142, 108.

Special Articles

ANÆSTHESIA IN THE CASUALTY DEPARTMENT

JOHN R. ROOK
M.B. Edin., D.A.
CONSULTANT ANÆSTHETIST, BIRMINGHAM ACCIDENT HOSPITAL

THE Birmingham Accident Hospital is in the heart of a busy industrial area with a large population, and deals with accidents at work, in the home, or on the roads, with sporting injuries, and with children hurt at play. About 50,000 new patients are treated each year, and the safe administration of anæsthetics, both general and local, in the busy casualty department requires considerable organisation and an established routine.

A routine has been built up and tested over the years 1941–51. During this time only one death occurred and was in no way concerned with the general anæsthetic being given at the time. Table I is an analysis of all anæsthetics, general and regional, administered during the year 1950.

The anæsthetic staff of the hospital consists of three consultants and two resident senior house-officers; the residents are regarded as trainees in anæsthesia. This team is responsible for the administration of anæsthetics in the main theatres of the hospital and in the casualty-theatres. Each day one consultant and one resident are on duty in the casualty department. The anæsthetists on duty are also responsible for the instruction of house-officers in the use of local analgesia, and they play a large part in the resuscitation of shocked patients.

Behind the organisation for the anæsthetic and surgical management of casualties is a short-stay ward—essential to the practice of the established routine—situated close to the casualty-theatres. This ward is partitioned, providing space for 16 male and 10 female beds (fig. 1).

TABLE I—ANALYSIS OF CASES IN 1950

General anæsthesia	*Cases*
Sepsis (digits, hands, &c.)	1942
Fractures:	
Arm	1124
Leg	299
Nose and jaw	71
Dislocations	211
Soft tissue injuries:	
Laceration sutures	417
Minor plastic repairs	178
Tendon repairs	33
Removal of foreign bodies	67
Others	85
Total	4627
Regional analgesia	
Minor lacerations (local infiltration and digital block)	11,570
Therapeutic and diagnostic blocks	313
Removal of foreign bodies	407
Brachial plexus block	110
Fractures (hæmatoma infiltration)	71
Total	12,471

The casualty-theatres are arranged as shown in fig. 2.

There are two large casualty-theatres catering respectively for "clean" and "dirty" cases which require a general anæsthetic or a more complicated regional block. Between the large theatres are a sterilising-room and a small theatre used for the suturing of minor wounds under local analgesia.

SHORT-STAY WARD

Let us follow the routine in a typical case. When the surgical staff have made an examination and written in the patient's case-record that operation is required, the patient is admitted to the short-stay ward. There he is seen by the anæsthetist who, after a general physical examination, decides in collaboration with the surgeon whether general anæsthesia or local analgesia would serve better. Two points receive special attention:

(1) The time of the last meal and the nature of the meal. No patient is given a general anæsthetic until four hours have elapsed since the last meal, unless the injury demands immediate surgical intervention.

(2) The time of the last meal in relation to the time of the accident. After an injury intestinal motility may be increased or, more frequently, inhibited. Thus, for the patient who has been injured shortly after a meal, four hours may not be long enough for the stomach to empty. In these circumstances a longer time is allowed to elapse before operation. The physiological upset after what is usually accepted as a trivial injury—e.g., a greenstick fracture of the radius—may be sufficient to delay the emptying of the stomach, and it has been considered necessary on many occasions to postpone the anæsthetic for five or more hours after the injury. This knowledge has been gained from experience—at times bitter experience.

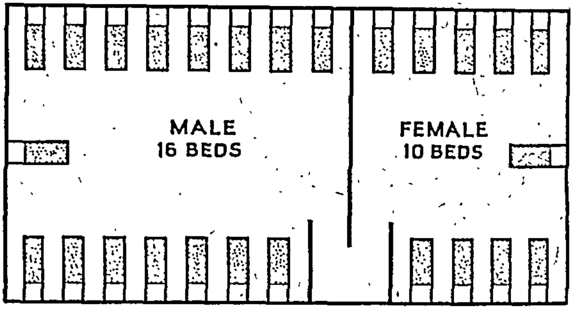

Fig. 1—Arrangement of short-stay ward.

All the patients are premedicated, generally with 'Omnopon' (papaveretum) and hyoscine, in a dose according to age. For simplicity the premedication chart shown in table II was produced incorporating five years' experience throughout the hospital.

The strength of the solutions in bottles A, B, and C was worked out in consultation with the senior pharmacist of the hospital and so calculated as to leave no residual solution after bottling (see appendix).

Before prescribing these drugs it is ascertained that no morphine has been given at a factory surgery or elsewhere before the patient arrived in hospital. In such an event only atropine is ordered. Omnopon and hyoscine are given sixty to seventy-five minutes before operation and atropine half an hour before operation.

CASUALTY-THEATRE

In the past nitrous oxide was the agent most frequently used for general anæsthesia in casualty departments throughout the country. Today the practice of "slashing" the septic finger of a jactitating and cyanotic patient, rendered unconscious by "dental asphyxia" or "surgical suffocation," is gradually dying out, but it is by no means extinct. The essence of such surgery was speed in conditions largely dictated by inadequate anæsthesia. In the Birmingham Accident Hospital we believe that the drainage of a septic finger or the reduction of a Colles's fracture should be carried out carefully and methodically under the best possible operating conditions, thus reducing the necessity for further operative procedures to a minimum. Therefore the aim in the casualty-theatre is that each patient requiring operation,

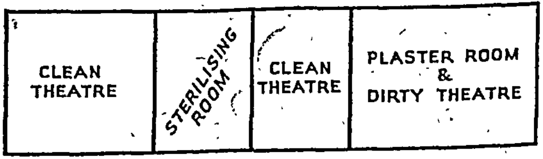

Fig. 2—Arrangement of casualty-theatres.

no matter how minor, shall have a skilfully administered anæsthetic.

The requisites in casualty anæsthesia are speedy induction, adequate depth, quick recovery, and absence of after-effects. Various drugs such as vinyl ether, cyclopropane, and trichlorethylene have been tried in combination with nitrous oxide/oxygen, but the nearest approach to the ideal has been found in thiopentone. The advantages of thiopentone/nitrous oxide/oxygen are ease of administration, elasticity of dosage, adequate relaxation, and complete absence of anoxia. The disadvantages are, firstly, the stimulating effect of thiopentone on the parasympathetic nervous system, with the danger of aspiration of vomit unless precautions are taken, and, secondly, complete recovery may not be very quick. However, the patient is able to regain his reflexes and sometimes consciousness before leaving the theatre, thereby preventing any untoward occurrence between the theatre and the ward, and the postoperative care by the nursing staff is facilitated.

As large numbers of cases receive an intravenous injection of thiopentone, certain precautions are taken to avoid intra-arterial or extravenous injection. An inflatable cuff with an aneroid manometer is placed around the patient's upper arm and the whole limb is immobilised on a board specially designed for the purpose. The cuff is then inflated to a pressure of 80 mm. of mercury and the intravenous injection is made (fig. 3). This manœuvre has the advantage of producing good veins for injection, and, providing the vessel is palpated for pulsation before injection, the possibility of injecting thiopentone into an aberrant artery is eliminated.

TABLE II—PREMEDICATION CHART

Bottle A:	Omnopon gr. 1/2	plus hyoscine	gr. 1/100	in 12 minims.
	,, gr. 1/3	,, ,,	gr. 1/150	in 8 minims.
	,, gr. 1/4	,, ,,	gr. 1/200	in 6 minims.
	,, gr. 1/6	,, ,,	gr. 1/300	in 4 minims.
	,, gr. 1/8	,, ,,	gr. 1/400	in 3 minims.
	,, gr. 1/12	,, ,,	gr. 1/600	in 2 minims.
Bottle B:	Omnopon gr. 1/3	plus hyoscine	gr. 1/120	in 12 minims.
	Not to be used for doses larger than omnopon gr. 1/15 plus hyoscine gr. 1/600.			
	Omnopon gr. 1/15	plus hyoscine	gr. 1/600	in 6 minims.
	,, gr. 1/18	,, ,,	gr. 1/720	in 5 minims.
	,, gr. 1/30	,, ,,	gr. 1/1200	in 3 minims.
Bottle C:	Omnopon gr. 1/7	plus hyoscine	gr. 1/280	in 12 minims.
	,, gr. 1/14	,, ,,	gr. 1/560	in 6 minims.
	,, gr. 1/21	,, ,,	gr. 1/840	in 4 minims.
	,, gr. 1/28	,, ,,	gr. 1/1120	in 3 minims.

Dosage for Age-group

Up to 6 mos.	Omnopon	gr. 1/30	hyoscine	gr. 1/1200.
*6 mos. to 1 yr.	,,	gr. 1/28–1/21	,,	gr. 1/1120–1/840.
*1 yr. to 2 yr.	,,	gr. 1/21–1/18	,,	gr. 1/840–1/720.
*2 yr. to 3 ,,	,,	gr. 1/18–1/15	,,	gr. 1/720–1/600.
*3 ,, to 4 ,,	,,	gr. 1/15–1/14	,,	gr. 1/600–1/560.
*4 ,, to 5 ,,	,,	gr. 1/14–1/12	,,	gr. 1/560–1/480.
5 ,, to 6 ,,	,,	gr. 1/12	,,	gr. 1/600.
6 ,, to 9 ,,	,,	gr. 1/8	,,	gr. 1/400.
9 ,, to 11 ,,	,,	gr. 1/7	,,	gr. 1/280.
12 ,, to 14 ,,	,,	gr. 1/6	,,	gr. 1/300.
14 ,, to 16 ,,	,,	gr. 1/4	,,	gr. 1/200.
17 ,, to 60 ,,	,,	gr. 1/3	,,	gr. 1/150.
60 ,, to 70 ,,	,,	gr. 1/4	,,	gr. 1/200.
Over 70 yr. ,,	,,	gr. 1/6	,,	gr. 1/300.

*According to build of child.

Age-groups 6 months to 5 years to have atropine gr. 1/200 in addition to omnopon and hyoscine 30 min. before anæsthetic.

As soon as the vein is punctured the pressure in the cuff is released, the syringe is fixed to the arm with adhesive tape, and thiopentone is slowly injected until the patient is asleep. The anæsthesia is continued with nitrous oxide/oxygen and the addition of half a litre of carbon dioxide to increase the speed of nitrous oxide saturation.

The mask is removed from the patient's face as soon as the operation is finished, and by the time the dressings have been applied or the plaster-of-paris has set, the patient has recovered his reflexes.

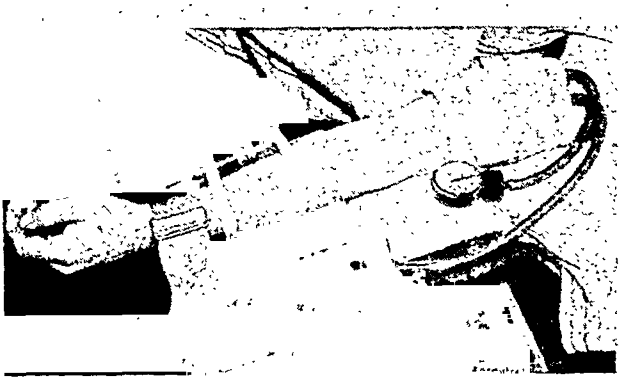

Fig. 3—Immobilisation of arm for intravenous injection.

For longer procedures, such as the manipulation of fractures requiring X-ray control, or the treatment of major septic conditions (e.g., exploration of a tendon sheath infection), it has been found desirable to continue the administration of thiopentone by fractional dosage.

The proportion of the population having chronic bronchitis is higher in industrial cities than in rural areas. When these people become casualties and need an anæsthetic, many of them start coughing violently during induction with thiopentone. Half a litre of carbon dioxide is a valuable adjunct to the nitrous oxide/oxygen in bringing the cough under control.

From time to time a casualty requires immediate operation—for instance when a fracture or dislocation occludes a main artery by pressure or traction. Prompt manipulation is essential to save the limb, and general anæsthesia, to give muscular relaxation, is necessary. The difficulty facing the anæsthetist is the likelihood of vomiting or regurgitation of stomach contents during anæsthesia in the unprepared patient. When there is the least doubt that the patient's stomach is not empty, an œsophageal tube is passed before anæsthesia is induced. A well-lubricated tube is passed through the nose and in most instances enters the œsophagus at the first attempt. The following sizes of tube have been found most suitable (equivalent sizes of Magill endotracheal tubes are also given):

	Œsophageal tube	*Magill tube*
Adult males (especially " drunks ") ..	18	7
Adults in general	16	5
Children over 4 years	12	2
Children under 4 years: Jacques urinary catheters are used.		

The practice of passing tubes through the nose avoids constriction by biting.

Often the patient vomits as soon as the œsophageal tube touches the pharyngeal wall, but otherwise all the fluid and some of the semi-solid contents can be evacuated from the stomach through the tube. Gastric lavage is then carried out until the washings are clear. This method of emptying the stomach may appear brutal, but it is the only safe way of preventing aspiration of vomit with its dangerous sequelæ. Morton and Wylie (1951) showed that anæsthetic deaths associated with regurgitation and vomiting were caused in 73% of cases by the inhalation of liquid vomitus.

The œsophageal tube is left in situ during induction. Atropine (gr. 1/200) is given intravenously before a small dose of thiopentone through the same needle. Thereafter the anæsthetic is continued with fractional doses of thiopentone and with nitrous oxide/oxygen. The anæsthetic mask is equipped with a hole and diaphragm for the stomach tube.

A number of closed fractures arrive in hospital with a fragment almost protruding through the skin. Unless manipulation is carried out in a short time the fracture will inevitably become compound. Our practice is to give intravenous pethidine (50–100 mg. depending on age and build). This gives sufficient analgesia for the limb to be gently manipulated and a guarding plaster applied. The patient is then admitted to the short-stay ward to await operation under general anæsthesia.

Special mention must be made of the young and the aged. The age-groups during 1950 are shown in table III. Of patients receiving a general anæsthetic, 25% were between the ages of 18 months and 14 years. The forcible administration of an anæsthetic is a terrifying experience for an unpremedicated child, and breeds nothing but fear of doctors and hospitals. Each child requires premedication and in addition to the customary dose of omnopon and hyoscine, pentobarbitone sodium ('Nembutal') may be given by mouth to the highly strung child. The following doses for children and adults given one hour before the anæsthetic are usually satisfactory :

TABLE III—AGE-DISTRIBUTION OF PATIENTS ANÆSTHETISED DURING 1950

Age (yr.)	No. of patients	% of total
0–1½	43	0·93
1½–7	579	13·0
8–14	569	12·28
15–70	3282	70·6
70–90	152	3·15
Over 90	2	0·04

0–1½	years :	Pentobarbitone not given.
*1½–3	,,	gr. ½.
*3–5	,,	gr. 1.
*5–8	,,	gr. 1½.
8–12	,,	gr. 2.
12–16	,,	gr. 2½.
16–60	,,	gr. 3.

* According to build of child.

Such preoperative treatment is only possible when a short-stay ward is provided.

Of the children under 7 who received a general anæsthetic, about a quarter had minor wounds which could have been easily repaired under local analgesia. But to avoid distressing them with needles, we admit them to the short-stay ward for premedication and preparation for general anæsthesia. This practice avoids mental anguish for the child, and prevents the screaming which upsets other patients. Adequate premedication followed by nitrous oxide and oxygen, given with suitable patter about magic wind and fairies, or a challenge to "blow up the balloon," is highly successful: thus with optimum conditions leading to a smooth induction, nitrous oxide/oxygen and 'Trilene' provide most satisfactory anæsthesia with minimal sequelæ.

For the aged patient a detailed physical examination is carried out. If there are no abnormalities of the cardiorespiratory system, a general anæsthetic is given. These patients often have a placid attitude towards minor operations and atropine alone is sufficient premedication. A minimal dose of thiopentone (0·1 g.) is followed by nitrous oxide/oxygen. When there are definite physical contra-indications to general anæsthesia, procaine by infiltration or regional block is used.

No patient who has had a general anæsthetic is allowed to go home alone.

LOCAL ANALGESIA

Most patients who had regional analgesia were operated on for small wounds. Infiltration with 1% procaine or digital block with 2% procaine were the methods used. No adrenaline was added to the procaine for finger blocks.

Therapeutic blocks were carried out for patients suffering from such injuries as broken ribs, when the pain was great enough to cause difficulty in breathing. Diagnostic nerve blocks were generally done at the request of the surgeon, and the patient came to the hospital by appointment. For example, simple nerve blocks were undertaken to assess the regeneration of a severed nerve in the forearm, the uninjured nerves being injected with procaine.

Brachial-plexus blocks were used for a variety of reasons, such as soft-tissue injuries of the arm and multiple injuries to fingers, when general anæsthesia was impossible because the patient had just had a meal, or when economic or domestic factors made it necessary for the patient to leave hospital as soon as possible. This method of regional analgesia was preferred to wrist block for hand surgery because it permitted the painless use of a tourniquet if required. Wrist blocks have been found ideal for hand surgery with finger tourniquets. A 2% solution of lignocaine hydrochloride ('Xylocaine') was found most successful; it acted more quickly and gave a more uniform result than procaine or amethocaine for brachial-plexus and wrist blocks.

With 3 exceptions the fractures reduced under hæmatoma infiltration were all of the Colles's type. Recently 2% lignocaine has been used and has given excellent results, superior to those with 2% procaine, which has not always given analgesia sufficient for the painless distraction of the impacted bone ends. This method was useful in old people, in patients with cardiovascular disease or diabetes, and when a large number of patients arrived on a frosty day.

The complete success of a regional block can easily be impaired by an ill-timed and audible comment by one of those present. To ask the patient, just after an incision has been made, whether he felt any pain may make him doubt the efficiency of the local analgesia and disturb his serenity. It is better to explain beforehand that he may be aware of being touched now and again, but that he will feel no pain. This is particularly important when little premedication has been given in order that the patient may leave hospital as soon as the block has worn off. If, despite these assurances, the patient is still agitated, intravenous pethidine (50–100 mg.) is very useful for allaying fear.

Emergency treatment of the acute chest injury calls for the closest coöperation between the surgeon and the anæsthetist. The severe pain of a crushed chest causes the patient to hold himself rigid, and the cardiorespiratory system soon becomes embarrassed by shallow respiration and the patient cyanosed. Such patients respond very well to intravenous procaine analgesia using a 0·2% solution in normal saline. This emergency measure relieves the pain and the resulting cardiorespiratory embarrassment. By overcoming the shallow respiration, it prevents the onset of further complications—namely, atelectasis and "wet lung" (Rook 1951).

SUMMARY

The importance of a short-stay ward for casualty patients is emphasised.

Preoperative physical examination and the prescribing of premedication should be carried out by the anæsthetist concerned. Routine premedication of children is important. Examples of simple and comprehensive premedication charts are given.

At least four hours should elapse after the last meal before anæsthesia is induced. If earlier operation is imperative the stomach should be washed out before a general anæsthetic is given.

Induction with thiopentone followed by nitrous oxide/oxygen prevents anoxia during anæsthesia and allows the patient to regain his reflexes before leaving the theatre.

My thanks are due to my surgical and anæsthetic colleagues Mr. F. G. Badger, Dr. L. J. Wolfson, and Dr. J. Birch for their most helpful criticism and friendly coöperation.

I am much indebted to Miss E. R. McNab, senior pharmacist to the hospital, for her help in constructing the premedication chart.

I am grateful to Mr. N. R. Gill and Mr. C. E. Richardson of the photographic department of this hospital for the diagrams and photograph.

REFERENCES

Morton, H. J. V., Wylie, W. D. (1951) *Anæsthesia*, 6, 190.
Rook, J. R. (1951) *Ibid*, p. 221.

Appendix

The omnopon-hyoscine solutions used are dispensed as follows:

Bottle A

Papaveretum	gr. 200
Hyoscine hydrobromide	gr. 4

1 in 1000 solution of *p*-chloro-*m*-cresol to 10 fluid ounces.

This quantity makes 10 one-ounce bottles.

The solution of *p*-chloro-*m*-cresol should not be stronger than 1 in 1000. A solution of 1 in 500 may precipitate the papaveretum. This does not apply to bottles B and C which contain much less papaveretum.

Bottle B

Papaveretum	gr. 40
Hyoscine hydrobromide	gr. 1

1 in 1000 solution of *p*-chloro-*m*-cresol to $7\frac{1}{2}$ fluid ounces.

This quantity makes 15 half-ounce bottles.

Bottle C

Papaveretum	gr. 40
Hyoscine hydrobromide	gr. 1

1 in 1000 solution of *p*-chloro-*m*-cresol to 7 fluid ounces.

This quantity makes 14 half-ounce bottles.

These solutions have been found to remain sterile up to one year.

BIRTHDAY HONOURS

THE list of honours published last week contains the names of the following members of the medical profession :

Baronet

Sir CECIL WAKELEY, K.B.E., C.B., D.SC. Lond., F.A.C.S., F.R.A.C.S.
President of the Royal College of Surgeons of England.

Companion of Honour

THE Rt. HON. WALTER ELLIOT, M.C., M.B. Glasg., F.R.C.P., F.R.S. M.P.
For political and public services.

K.C.B. (Military)

Lieut.-General Sir NEIL CANTLIE, K.B.E., C.B., M.C., M.B. Aberd., F.R.C.S.
Lately director-general, Army Medical Services.

Knights Bachelor

WILLIAM ERRINGTON HUME, C.M.G., M.D. Camb., F.R.C.P.
Lately senior physician to the Royal Victoria Infirmary, Newcastle upon Tyne; emeritus professor of medicine.

EDGAR LAURENT, C.M.G., M.D.
For public services in Mauritius.

Group-Captain HUGH RAYMOND GUY POATE, M.V.O., CH.M. Sydney, F.R.C.S., R.A.A.F.
Consulting surgeon, Royal Prince Alfred Hospital, Sydney.

C.B. (Military)

Major-General ARNOLD GUY HARSANT, O.B.E., M.D., M.S. Lond., F.R.C.S., Q.H.S.
Director of Surgery, War Office, and consulting surgeon to the Army.

Air Marshal JAMES MACCONNELL KILPATRICK, O.B.E., M.B. Belf., Q.H.P.
Director-general, R.A.F. Medical Services.

Surgeon Rear-Admiral THOMAS MADILL, O.B.E., M.B. Dubl., Q.H.P.

C.M.G.

CHARLES WILCOCKS, M.D. Manc., F.R.C.P.
Director, Bureau of Hygiene and Tropical Diseases.

C.B.E. (Military)

Air Commodore FRANCIS WILFRID PETER DIXON, M.B.E., M.B. Melb., F.R.C.S., R.A.F.
Consultant surgeon to the R.A.F.

Surgeon Captain ERIC SNOW MCPHAIL, M.B., R.N.Z.N.

Surgeon Captain JOHN GEORGE MAGUIRE, M.B. Dubl., R.N.

Brigadier ALBERT SACHS, M.D. Dubl.
Director of Pathology, War Office, and consulting pathologist to the Army.

C.B.E. (Civil)

Colonel ALDINGTON GEORGE CURPHEY, M.B.E., M.C., M.D. Queen's Univ., Ont.
For public services in Jamaica.

Colonel WILLIAM ROBERT MACFARLANE DREW, O.B.E., M.B. Sydney, F.R.C.P.
Lately professor of medicine. Royal Medical College, Bagdad.

JOHN JOSEPH HOLLAND, M.B. Sydney, F.R.A.C.S.
For public services, especially in connection with the ambulance service, in Western Australia.

ANDREW BUCHANAN MACDONALD, M.B.E., M.B. Glasg.
Lately superintendent, Itu Leper Colony, Church of Scotland Mission. Nigeria.

SYDNEY ALAN STORMER MALKIN, M.B. Lond., F.R.C.S.
Orthopædic surgeon, Mansfield and District General Hospital; vice-chairman, Portland Training College for Disabled.

ALAN AIRD MONCRIEFF, M.D. Lond., F.R.C.P.
Nuffield professor of child health, University of London; physician to the Hospital for Sick Children, Great Ormond Street.

WILLIAM RITCHIE RUSSELL, M.D. Edin., F.R.C.P.
Neurologist to the United Oxford Hospitals; consultant neurologist to the Ministry of Pensions.

WILLIAM JAMES STUART, M.B. Edin., F.R.C.S.E., F.R.S.E.
Consulting surgeon to the Royal Infirmary, Edinburgh; chairman of the executive committee, Scottish National Blood Transfusion Association.

O.B.E. (Military)

Wing-Commander ANTONY JOHN BARWOOD, M.R.C.S., R.A.F.

Colonel EDWIN WILLIAM HAYWARD, F.R.C.S.E., R.A.R.O.

Surgeon Commander DERMOT FRANCIS WALSH, M.B. Dubl., R.N.

O.B.E. (Civil)

LLOYD OSCAR ABEYARATNE, M.R.C.P.E., L.M.S.
Medical officer, Hospital for Women and Children, Colombo.

Alderman ALBERT CAMPBELL, L.M.S.S.A.
Mayor of Accrington, 1951-1952

GEORGE CHESNEY, M.D. Belf.
Medical officer of health for Poole.

HERBERT EMERSON, M.C., M.B. Dubl.
Senior medical officer. Ministry of Pensions.

GEOFFREY JASPER ST. CLAIR FISHER, M.B. N.Z.
Gynæcologist to the Auckland Hospital, New Zealand.

WILFRED VIVIAN HOWELLS, M.B. Camb.
Anæsthetist to the Swansea Hospital; member of the Central Health Services Council.

JOHN JOSEPH LANDERS, M.B. N.U.I.
Principal medical officer, H.M. Prison Service.

(Miss) MABEL GORDON LAWSON, M.B. Aberd., D.N., S.R.N.
Deputy chief nursing officer, Ministry of Health.

NOEL SPENCER NAIRNE, M.R.C.S.
Medical Officer, Ministry of Transport.

MAHAPITIYAGE VELIN PETER PEIRIS, F.R.C.S.
Visiting surgeon to the General Hospital, Colombo.

DENYS HENRI RENÉ VOLLET, M.B. Cape Town.
Director of medical services, Basutoland.

M.B.E. (Military)

Major STEPHEN OLIVER BRAMWELL M.B. Edin., R.A.M.C.

Lieutenant KEITH ERNEST GOREY, R.A.A.M.C.

Major JOHN LUDLOW WHITMORE, M.R.C.S., R.A.M.C.

M.B.E. (Civil)

JUSTIN AELIAN FERNANDO, L.M.S. Ceylon.
Medical practitioner, Colombo.

WILLIAM DAVID STONEY JOHNSTON, M.D. Edin., F.R.A.C.S.
For services to the community in Nelson, New Zealand.

(Miss) CAROLINE BAXTER KIBBLE, M.R.C.S.
Medical officer, Colonial Medical Service; lately temporary medical officer to the Malay Regiment.

(Mrs.) JOYCE REWCASTLE LUDLOW, M.B. Lond., F.R.C.S.
For medical and social welfare work in Nigeria.

GEORGE FELIX RANDEGGER
Medical adviser to H.M. Embassy and to the British community in Rome.

Points of View

WHAT IS WRONG WITH CANCER RESEARCH?

MALCOLM DONALDSON
M.B. Camb., F.R.C.S., F.R.C.O.G.
LATE DIRECTOR, CANCER DEPARTMENT, ST. BARTHOLOMEW'S HOSPITAL, LONDON

THE answer to this question is simple: there is not enough of it. To the further question, "Why should that be so?" the answer is much harder to find. There is no lack of problems connected with cancer which need to be solved—indeed, the number seems infinite—but, when the heads of laboratories are asked why more is not being done, various explanations are given. Perhaps the most common is that people capable of doing research are not available. Others say that they receive many applications from people whom they would like to accept, but they have no room. Yet another answer is that there *is no money.*

Surely these difficulties can be overcome. It is rather astonishing that a disease with a mortality of 85,000 a year should arouse so little "official interest." Until a few years ago the cancer "branch" at the Ministry of Health seemed to consist of one part-time man. When the Medical Research Council was set up we were told that it would not touch cancer, because there were so many other problems whose solution was considered more possible—e.g., rickets. This was, of course, an understandable decision at the time, and at present a considerable amount of cancer research is being carried out by the M.R.C. through various teams. Under the National Health Service Act research can be undertaken *in the hospitals.* All other cancer research, however, depends on voluntary efforts supported by voluntary contributions.

PAUCITY OF CAPABLE RESEARCH-WORKERS

There is nothing surprising in this answer, because the head of the department looks for a man or a woman who is already experienced. The problem is how can more people be trained in order to become experienced?

First, we must consider how at the present time a person becomes a research-worker. Inquiries suggest that the process is very haphazard. The desire to do research is fairly common among medical students, but the zeal for it soon disappears when the difficulties to be overcome are realised. Laboratory posts and registrarships entail a great deal of routine work, and any effort to do research has to be made "after hours," when the worker is tired out. He is, of course, given kindly advice by his seniors, and may show himself to be exceptionally talented; but the outlook is bleak, and many people wishing to get married and settle down throw up the sponge or take some teaching post in the hope that they can do some investigation. This hope soon recedes, but if the man is very keen and fortunate he will transfer to a post in a research institution.

Many will approve of this method of selection by the "survival of the fittest"; but it entails a great loss of potential research-workers. The suggested remedy is to create a "medical-research profession or specialty," paid for out of a State grant. To enter this specialty a minimum of four years' training would be required after medical qualification. In exceptional cases non-medical candidates might be admitted. During the first two years the candidate would be put on a research problem chosen by the head of the department and would obey orders. If at the end of this time, or possibly earlier, he was considered to be below standard he would cease to have official paid training. During the next two years the candidate would have some say in the choice of his research, and might work for a higher science degree, but he would still be under supervision. At the end of four years he would be a qualified research-worker. It is obvious that there will be few candidates for this "profession" or "specialty," unless they are paid a living wage during their training and sufficient well-paid posts are created to give some guarantee of a decent living in the future.

It may be objected that research-workers, like poets, are born and not made; but even poets have to be taught to read and write. Two years in a subordinate position will do no harm to a good man, and the work done would relieve his senior of some of the "drudgery" of his own research.

LACK OF ROOM AND FUNDS

Then there is the second objection raised—namely, that the best-known laboratories have no room for the people who apply. But how many such laboratories are there? The remedy is to have research laboratories *attached to every general hospital.* This, of course, brings up the third objection—insufficient money. Surely the time is past when the greater part of cancer research must depend on voluntary contributions. The Treasury must provide more money for this purpose, possibly through the University Grants Committee or through the Medical Research Council.

From time to time questions are asked in parliament, the latest being on March 30, 1952, when the reply received was "that the Ministry of Health has this question constantly under review in consultation with the Medical Research Council. It was estimated that more money would be spent in this financial year on certain developments which would be in the interests of research as well as treatment." How illuminating! Is it to be sixpence more or a shilling? Very few people would grumble at public money being spent on cancer research.

COÖRDINATION

Another crying need is some coördinating body. There is in existence a Radiotherapy and Cancer Committee, whose duty is to advise the Minister. I know little of what it does, but hope that it may develop as the *Radium Commission* did up to the time of the 1946 Act. That body started as a sort of "quartermaster's stores" for radium, but developed into a coördinating body for all radiotherapy centres in the country. The coördination was achieved by periodic visits to the centres, when the experts on the commission were able to talk with and advise their colleagues in the various centres. In addition, the doors of the commission were always open for advice and consultation, and the results obtained were really remarkable. This did much to raise the standard of radiotherapy in this country to a position second to none.

CLINICAL RESEARCH

So far reference has been made only to laboratory cancer research. The problem of clinical cancer research is much more difficult, and indeed at present seems insoluble. The difficulty is fundamental, because very few good clinicians have the ability or desire to do research. Good clinicians are individualists, whereas in research team-work is *essential.* On the other hand, clinicians keen on research are apt to be poor clinicians. Few clinicians have the time or desire to make records which will be of statistical value in years to come: they only make sufficient notes to remind them about the conditions of the case next time they see the patient.

Added to this, there is little or no coöperation between different institutions; indeed often there is acute rivalry. Few institutions see enough cases of any particular type of cancer to make statistics of real value, and even in the same institution the cases are divided up between individuals who seem to have great difficulty in collaborating.

However, laboratory research is the more important and should be expanded. Money itself will not bring the solution of the cancer problem, but without it the secret will never be solved.

Medicine and the Law

The Label on the Bottle

STATISTICALLY the proportion of fatalities due to preventable misadventure in hospital practice must be small enough in comparison with the routine cases where carelessness is avoided. Publicity for such incidents as the following may help to make it smaller still.

A patient was admitted to hospital with subacute intestinal obstruction. The specialist surgeon decided to operate. In the course of the operation he directed the senior house-surgeon to give an intravenous infusion of saline solution: the latter asked the theatre nurse for a bottle of saline. A student nurse, taking the message, went to the sink, took the bottle which she thought contained normal saline, put it at the bottom of the trolley which was being used for the infusion, and went back to her work. A second student nurse, who had been training for 3½ years, took the bottle and held it towards the house-surgeon, who inserted the giving set into the bottle. About two minutes later he noticed that the patient's arm was dusky; three minutes afterwards he noticed that there was writing on the bottle and that the label read "10 per cent. formaldehyde." He stopped the transfusion immediately and told the operating surgeon, who, observing a rapid deterioration in the patient's condition, ended the operation as soon as possible. Death occurred almost at once after the patient had been removed from the theatre.

The coroner for Stamford and district, recording a verdict of accidental death, commented that the accident arose from carelessness and should never have happened. Had formalin not been put into a normal-saline bottle, it probably never would have happened. If the nurse handling the bottle had taken the elementary precaution of reading the label before the bottle was used, it would not have happened. The coroner added that he did not propose to apportion blame, but he had no doubt that the hospital authorities would so order their affairs in future that there could be no recurrence of so regrettable an accident.[1]

Obituary

DR. JOHN WHARTON

S. T. C. writes: "Johnnie Wharton, as he was affectionately called, was one of our characters in the Manchester medical school. He was an excellent teacher, and took endless trouble to see that good students knew something of eyes before he finished with them. Small in stature, he wore half-moon spectacles; when he looked up at you, there always seemed to be a twinkle, for he had an impish humour. He divided students into good and bad; if you were in the 'good' category, you became a friend and were told of adventures that befell him in his student days at the hands of Lloyd Roberts. We shall long remember him, as a humane man, and a typical Lancastrian."

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[1] *Yorkshire Post*, May 30, 1952.

In England Now

A Running Commentary by Peripatetic Correspondents

WHEN I send a patient to outpatients I always write a letter. It is as nice a letter as I can make it. Ceremonious and polite, with (I hope) just the right tinge of deference and admiration for the consultant's attainments, and with just enough cri-de-cœur to move his bowels to compassion for my ignorance. "Good fellow this," he says (I hope); "Doesn't know anything of course. But tries hard. Takes any amount of trouble."

My letters are beautifully typewritten, with the patient's name, address, and age at the top, and all spelt right.

I feel this sort of letter is what a consultant really needs. Not for the information in it, which he can usually get for himself anyhow, but for a psychological reason. It is really a form of propitiation. Apart from its obvious recital of facts, it really says: "I know I am making you work, and I am sorry. But this nice long typewritten letter proves that I have worked too. I have done my feeble best, and I am beaten. You are a cleverer man than I, please help me."

Even specialists of the eye, the ear, nose, and throat, *and the rectum—breeds notoriously independent* of medical histories—are sticklers for the punctilio of the full-dress letter. I had a pointed reminder of that from an eye specialist recently. I sent him a patient with a brief, hurried, rather untidy note of the "Grateful for your help with this patient" sort. He returned it in its own grubby envelope on the back of which he had written very neatly "I received this from you today" with a curt diagnosis and prescription. He was returning it with a pair of tongs.

I was duly ashamed and now type him letters at length, carefully composed, with the date the eye first felt sore and all the minutiæ of symptoms and treatment. Quite unnecessary of course, and I don't suppose he reads them all through; but he likes them, for he now replies with full details and old-world courtesy. He sees I have taken a lot of trouble and he is satisfied. I am satisfied too. I am practising hard at the typewriter and I must write *something.*

* * *

We have grown accustomed to hearing complaints from our teachers that this or that subject (their own) is sadly neglected in the curriculum, but one subject for which I have so far noticed no plea is the study of *The Touch.* Yet those unacquainted with the condition are powerless against an attack and their chance of recovery is almost nil: whereas with adequate prophylaxis complete immunity can practically be guaranteed.

I speak with authority here, for I have probably suffered from this complaint more often and under more varied forms than any of my colleagues living or dead. In proposing myself for the post of lecturer, which will no doubt shortly be instituted, I should like to give a brief résumé of the course I have planned for postgraduates. For the undergraduate I can promise no more than a safe-conduct past the most elementary attempts on his capital. To repel the more vicious attacks he will have to await experience and maturity; but fortunately he is unlikely to encounter such attacks until he becomes financially vulnerable.

My course would be compulsory, exemption being granted only to intrepid characters who could satisfy the examiners that their intangibility was at least equal to that of the Untouchables' patron saint, Mr. Seth Pecksniff, as exhibited in his classic victory over Mr. Montague Tigg, the leading Toucher of all time.

My first lecture would be on *The Inevitability of the Touch.* Many a young man has suffered such mortification, and had his faith in human nature so brutally shaken, by his first sudden unexpected Touch that he has fallen into a life-long melancholy. I would show that the Touch is now as inevitable as were the unpaid bills of the bad old capitalist days, before the National Health Service brought us a reputation for touchable affluence. When its inevitability has been fully accepted, and attempts at a Touch excite no emotion beyond pleasurable interest and expectation, I should turn to the various defence mechanisms available to the student and describe the several types of Toucher; next I should recount and analyse some typical Touch stories—"The baby threw my purse in the fire." "My note-case slipped out of my hand down a drain." "I haven't had a bit of food since Thursday." &c. Here the student would embark on practical work with a series of Chronic Touchers specially engaged to exercise his growing knowledge. In the event of failure no money would be returned.

Next we should study the Touch Compulsory, where the student manœuvres a patient into touching him when he had no intention of so doing. The first axiom of Touching will explain why—simply that once the Touch is concluded *the Toucher is never seen again.* We all have patients we would gladly never see again, so the chance of perpetual immunity for a modest outlay should not be missed. I have been approached by some students, obviously possessing great natural gifts, with the suggestion that a special prize might be awarded to candidates who extend the Touch Compulsory to the point of effecting a Touch on a would-be Toucher. I have set my face against such proposals. Attack must remain in essence a defence. *Attaquer pour mieux reculer, et surtout pas de zèle.*

Modesty forbids me (unless urged) to give details of my own successes. And I have had my failures. One cannot be perfectly protected at all points. New techniques of Touching are constantly being evolved, for science never stands still. Even a sudden reversion to primitive methods may score an unwelcome success. Just as princes of the turf have fallen victims to a three-card trickster or a common thimble-rigger, so the advanced student who enjoys a good laugh over a story of ruin on the Stock Exchange may succumb feebly to a pedlar of gold bricks, or a hawker of Spanish treasure. Humility here, as in all branches of knowledge, must be our guiding star.

* * *

Students of *In England Now* who have followed our quest for a bat for experimental purposes may well suppose that we ended with a surfeit of bats. In our communiqué of June 7 the matter was in the hands of our experienced and capable Animal Man, and we had no fear for the future—we had but to visit the Church of the Stuffed Owls and scoop up handfuls of bats.

We set off with light hearts, armed with a rat cage, a sack, a powerful torch, and some leather gloves as a protection against bat-scratch fever. The church was small and whitewashed, and the roof timbers irregular enough to hold a profusion of bats; perched insecurely on the walls were the stuffed owls, putting as nonchalant a face on it as possible. We searched the lower levels systematically, hunting for guano between the pews and the walls, shining our torch inquisitively under the base of the pulpit, and carefully examining the bottom of an empty brandy bottle. We found traces of many pigeons, but no bat spoor; so we retired to the farm to borrow a ladder to inspect the higher reaches of the chancel. Here we struck a snag: the ladder was at present preventing the egress of a number of large and active pigs, and it appeared that the difficulties of our bat-hunt were as nothing to those of the pig-hunt that would result if the animals ceased, even temporarily, to be confined. We learnt that Incense is Best for Bats, but also that we had underestimated the bat-repellent activity of the stuffed owls. It was doubtful if even a single bat remained. Crestfallen, we withdrew to collect our impedimenta, touching our hats respectfully to the owls as we left.

We are still on the trail. Specimens are being reported to us from distances up to 15 miles, and only yesterday we heard of a house in Eire where 300 bats were caught last year. Our travel grant might just run to that.

* * *

News from School.—"This is what I did on Long Leave Day: Train to Paddington (7*s.* 6*d.*), bus to Charing ✠ (5*d.*), water bus to Tower Br. (9*d.*). Walked about and watched the Bridge open. We were just beside the guns when the 62 (?) shots were fired for the Queen's birthday. Went back to Charing ✠ (9*d.*), tube to Regents Park (8*d.*), Zoo (2*s.* 6*d.*), Aquarium (1*s.*) (?), tea, &c. (3*s.*) (?), tube (8*d.*). And so it came to quite a lot of money."

Letters to the Editor

APPOINTMENT SYSTEMS IN HOSPITAL OUTPATIENT DEPARTMENTS

Sir,—After reading the article by Brigadier Welch and Mr. Bailey (May 31) I must confess to feeling some disappointment.

It is commendable that they should seek ways of reducing the waiting period in outpatient clinics, but one cannot help feeling that they have taken too mathematical a view. Although they suggest that "it is not reasonable to carry this comparison too far," it is a somewhat sad commentary on the times that they do compare at all a ladies' hairdressing establishment with a consultative clinic. At the hairdresser's, they state, "the discipline of staff and customers is strict"; and, while I have no wish to ascribe to them a meaning which they did not intend, some administrators may clearly be tempted to conclude that a tightening of discipline in hospitals will produce "efficient" results.

In my experience it is extremely difficult to give any accurate idea of the time required for consultation, if each patient is to be given the benefit of a considered opinion. I have no doubt that many consultants could work more strictly to a time-table, but I am equally sure that, where they do, the quality of their work may suffer: Brigadier Welch's figures improve, but the standard of service—that elusive quality which is not measurable statistically—will go down.

An important aspect of the appointment system, not mentioned by your contributors, is that it may lead to undue delay in getting the patient to the consultant, and this is especially true when a limited number of new appointments is set for each clinic. Some hospitals and consultants are more responsive to the needs of the local practitioners, and they try to avoid any strict limit on the number of new patients seen. In these circumstances there are sometimes unavoidable delays at the clinic but the patient has the immeasurable advantage of attending hospital after little or no delay. I would submit that most patients would prefer, where possible, to be seen at the next consultative clinic even at the cost of an hour's waiting.

Far be it from me to decry the invaluable discipline of statistics; but pray let us protect Medicine from well intended statistical surveys which may encourage tidy minded administrators to forget that the quality o service and the preservation of the doctor-patient relationship are our prime concern.

R. S. MURLEY.

Radlett, Hertfordshire.

Sir,—In the article by Brigadier Welch and Mr Bailey the punctuality of patients is analysed and favourably commented upon, but no very adequate analysis is made of the number of patients who book appointments and then default. I have worked in clinics where at times defaulters represented 25% of the whole This suits me, as I am a lazy type and enjoy teaching *students during waiting periods;* but it demonstrates the indifference of a section of the community towards a hospital service that tries to help patients by an appointment system.

An analysis (not statistical) of reasons for patients not turning up gave the following answers: (1) forgot (2) got better, (3) missed the bus, (4) went to the wrong hospital, (5) went to the cinema, (6) mind your own business. The suggestion that the booking clerk should have been informed by telephone that the appointment could be cancelled was regarded by 100% o those questioned as undemocratic and a waste o money.

J. C. HAWKSLEY.

London, W.1.

SIR,—Having scarcely recovered from the flagellations by Professor Titmuss,[1] we have now to face the results of yet another apparently lay investigation.

At last, it appears, the cause of outpatients waiting has been discovered. The solution is given. As a statistical review it is, no doubt, unexceptionable. Applied to so human an undertaking as an outpatient clinic it seems to assume the form of an exercise in intellectual speculation.

Let us look a little closer. First let us pay tribute to the investigation that led to the remarkable discovery that we are unpunctual. We are instructed how to work out, by a process of arithmetic not beyond the powers of the average consultant, the consultation-time per patient. By so doing we can avoid patients having to wait. One is captivated by the very ingenuousness of the theory. How about the practical application ?

1. To examine one individual may take 5 minutes. To do the same for another may well take twice that time, although the complaint is the same. Each requires a different approach. A child may require time and patience, and these must be given, in spite of the statistician's time-table.

2. Has it occurred to the authors that (especially in the specialties dealing with emergency work) one's time-table can be somewhat dislocated by urgent work ? After a long morning clinic a visit to the ward to deal with some particular problem may spell lateness for the afternoon.

3. Finally may I refer to what is probably the most preposterous suggestion of all—why must a long consultation, involving perhaps a colleague, be kept until the end ? Would it not be better (and here I mean for the patients and not for our stop-watch-armed mentors) for the business to be dealt with on the spot ? It might astonish our experts to learn that the homely reason for this is a human one : our colleague may have gone home.

Spare us, Sir, these profitless speculations. This itch to express in terms of figures activities of hospital life is distressing. Is it, I wonder, another manifestation of that malady to which Grant Waugh recently drew attention—namely, " pseudo-scientific meticulosis " ?

Ipswich.   T. DENNESS.

SIR,—I read with interest the article by Brigadier Welch and Mr. Bailey.

Antenatal clinics at hospitals are probably among the most time-consuming from the patient's point of view. Three and a half years ago I attended the antenatal clinic at a well-known maternity hospital.

There was no appointment system in operation, and every patient was told to be there at 9 A.M. By 9.30 the waiting-room was full to overcrowding. Consultations never appeared to begin before 9.45 A.M., and one could account oneself lucky to get away by 11.30 A.M. On a first visit, which meant a history, examination, and visit to the almoner, it was more likely to be 1 P.M. Patients were divided roughly into two groups—those who had to undress and those who had not, the latter requiring only weighing, blood-pressure reading, and urine analysis. There was always a good deal of confusion over this division, and patients were always finding themselves in the wrong queues. One of the saving graces of this clinic was a small canteen supplying tea and buns for a few pence—most welcome to patients like myself whose nausea was aggravated by hunger.

Currently I am attending the antenatal clinic at another hospital.

Here there is an appointment system of a very curious kind in operation. I telephoned to make an appointment and was told 10 A.M. This clinic has an outer room with a clerk in attendance, and incoming patients sign their names in a book. As their turn came their names were called and ticked off in the book. About 11.30 A.M. I noticed that a number of women who had come in after me had been called. I went and looked at the book and saw that patients who had signed after me had been ticked off. I queried this with the clerk, who said : " It usually takes a bit longer if you have an appointment." I am still wondering why this should be the case.

Being now thirty-two weeks pregnant I have reached the undressing stage. After about an hour in the waiting-room names are called in batches of four or so. We undress in cubicles, and, donning the dressing-gowns provided, sit on little stools until called for examination. On the last occasion I noticed that women who came in my batch had been seen and had dressed and gone while I and one other still waited. After thirty-five minutes of sitting in a communal dressing-gown I asked the sister if I were being forgotten. She explained very kindly that some patients were seen by the consultant, some by the registrar, and some by the midwives. There was only one midwife available that morning, whom I was supposed to see ; and she also had to look after the weighing of other patients and pass them on to the appropriate doctor.

All patients attending these clinics are housewives whose mornings are normally fully occupied with housework and shopping. Many have to bring small children with them to the clinics, where they become bored, restless, and irritable. There are no facilities for amusing them or having them looked after while the mother is examined.

In the earlier stages of this pregnancy I attended the local-authority antenatal clinic, which compares very favourably with the hospitals'.

In the first place it is held in the afternoon, which is much more convenient for most mothers. The appointment system worked fairly well, and delay occurred only when there was a sudden influx of new patients. When this happened the very efficient and courteous reception clerk was most apologetic. Chairs stood round the walls in place of the usual benches, which left a space in the middle of the room where toddlers accompanying their mothers could play. A few toys had strayed in—perhaps from the neighbouring child-guidance clinic. The atmosphere was much more friendly and informal than at the hospitals.

In antenatal clinics the length of consultation is relatively easy to predict. I earnestly plead on my own behalf and for countless other mothers that something should be done to stop this inordinate waste of time.

Kingston-on-Thames.   ROSEMARY STANFORD.

RECOVERY WARDS

SIR,—With reference to the article by Dr. Davies and Dr. Hunter (April 26), I experienced the value of a recovery ward when I was stationed at Bir Yacow Military Hospital in Palestine (at other times known as the 12th British and the 15th Scottish Military Hospital). This 1200-bed hutted hospital was originally built at a time when dispersal was thought to be the best protection against air-raids, and some of the wards were more than half a mile from the operating-theatres. Accommodation had, therefore, to be provided close to the theatres where ambulances could deposit lying patients previous to operation and from which they could collect them afterwards. One hut was built contiguous to the theatres and directly connected to them by a short passage-way. It was furnished with a nominal 24 beds which were supernumerary to the normal bed complement and which did not appear on any bed list.

This ward, although primarily intended only as a collecting and dispersal point, was, in fact, the making of the hospital from the surgical point of view. It served not only as a recovery and resuscitation ward where all necessary equipment could be concentrated and immediately available, but for many other purposes when patients required special care. Having once experienced its value, no member of the staff, whether medical or nursing, had the slightest doubt that such a ward should be available in every general hospital :

1. Operation cases were transferred to this ward well before the time of operation so that all preoperative preparations could be carried out by an experienced staff under the

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[1] See *Lancet*, May 17, 1952, p. 1014.

best conditions and under the close supervision of the anæsthetist, and the patient could wait in comfort until his turn came.

2. All facilities for resuscitation were available, and post-operative patients could be retained here until they were completely fit to return to their wards.

3. Patients requiring frequent dressings under anæsthesia could be held here for a few days so that they had the minimum disturbance on their journeys to and from the theatre.

4. Emergencies could be admitted direct to this ward, prepared, retained after operation (overnight if necessary), and only sent to one of the permanent beds the next day; thus avoiding the disturbance of all the other patients which is inevitable when an emergency is admitted at night or during meal or visiting times.

5. In the event of a mass influx of patients, a number of beds were immediately available which, by placing mattresses on the floor, could be supplemented to any desired extent without in any way disturbing the general run of the hospital. On one occasion at Bir Yacow, 53 soldiers, severely injured by the mining of a train, were admitted and being resuscitated within half an hour; similar unexpected mass disasters are not so very uncommon in civil life.

6. Because the ward was in such close proximity to the theatres, the surgeons and anæsthetists could exercise the closest surveillance of the patients, and there were very few hours in the twenty-four when a doctor was not within hailing distance, if not actually present in the ward.

7. But the greatest advantage of such a ward lies in the saving it effects in skilled nursing and the relief it affords to the ward sisters. By ensuring that it at least has an adequate trained staff and that patients are never returned to the general ward until they have completely recovered from their anæsthetic or been adequately resuscitated, the main strain on a surgical ward sister is removed; and it will be found that she can manage with fewer and less experienced staff without any harm coming to her patients.

Although long familiar with the principle of resuscitation/recovery wards, it is only since working in a hospital which had one that I have fully appreciated their great value. Even if only a wooden hut (as it was in this case), provided it is in the closest proximity to the theatres and has beds which do not figure on the bed-return, its value to the surgical patient and to the hospital is inestimable.

University College of the West Indies,
Mona, St. Andrew, Jamaica.
G. H. C. OVENS.

A.C.T.H. AND THE PIGMENT HORMONE

SIR,—Your annotation last week suggests, on the basis of the work of Johnsson and Högberg[1] and of Sulman,[2] that A.C.T.H. and intermedin are identical and that the melanophore-expanding action may be used for the bio-assay of A.C.T.H. Actually the two hormones are not identical, and the melanophore effect is of no value for the assay of A.C.T.H. The evidence for this is:

1. It has been known for many years (Waring and Landgrebe[3]), that the biological potency of intermedin is actually increased by heating with 0·1 N NaOH, whereas A.C.T.H. activity is rapidly destroyed by this reagent even at room-temperature.

2. Intermedin can be obtained free of A.C.T.H. potency by the carbon adsorption process of Landgrebe, Reid, and Waring.[4]

3. A.C.T.H. can be obtained free of intermedin activity by counter-current distribution between sec.-butanol and various aqueous acid solutions.

The close similarity in properties of these hormones has been known to workers on the chemistry of A.C.T.H. for some time, and there is little doubt that the melanophore-expanding effects observed by various workers in A.C.T.H. preparations are due to contamination.

Endocrine Unit,
The London Hospital,
London, E.1.
C. J. O. R. MORRIS.

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1. Johnsson, S., Högberg, B. *Nature, Lond.* 1952, 169, 286.
2. Sulman, F. G. *Ref. Veternarith.* 1952, 9, 31.
3. Waring, H., Landgrebe, F. W. The Hormones, ed. Pincus Thimann. New York, 1950; vol. 2, 427.
4. Landgrebe, F. W., Reid, E., Waring, H. *Quart. J. exp. Physiol.* 1943, 32, 121.

PLACENTAL CONTENT OF A.C.T.H.

SIR,—In an annotation (Feb. 16, p. 354) you ask whether the placenta can produce A.C.T.H.

Last year we ground and dried fresh human placental tissue from a 12-week pregnancy, and extracted the powder with physiological saline solution containing 0·25% acetic acid. The A.C.T.H. content of this extract was tested by Sayers's ascorbic-acid depletion method.[1]

Thirteen hypophysectomised rats were treated with 0·5 ml. of the extract (equivalent to 0·5 mg. dried placental tissue per 100 g. body-weight of the animal). The result, however, was completely negative; the average depletion in ascorbic-acid content was only 6 mg. per 100 g. adrenal tissue.

We have also tested the content of A.C.T.H. in the rat placenta with a similar negative result.

This result has since been confirmed in tests on 7 human placentæ, of which 2 were from early pregnancies, 1 from a 30-week pregnancy, and 4 from full-term pregnancies.

Research Division,
Nyegaard & Co. A/S,
Oslo.
F. BÖE
S. SALVESEN.

FIESTA IN PAMPLONA

SIR,—I read with pleasure and interest your peripatetic correspondent's commentary on this subject (April 19). I wish to state, however, that the present fashion of doing the muleta work close to the bull started long before the use of antibiotics. Furthermore to believe that knowledge of the better prognosis of horn-wounds can influence the style of bull-fighting is to know the Spanish temperament but poorly.

Instituto Investigación Científica,
Caracas, Venezuela.
MARCEL ROCHE.

RHESUS NOMENCLATURE

SIR,—CDE-cde blood-grouping is the basis of a large and expanding body of information which is of great importance and interest to serologists and geneticists, but apart from research it is needed in only a small fraction of 1% of cases: in all other instances only CDE grouping (see accompanying table) is required, or is, indeed, possible. In view of this and of the fact that anti-C and anti-E sera are already available commercially in America, can Dr. Wiener really maintain (April 26) that it makes confusion worse confounded to suggest that what the general medical public needs to know about the CDE blood-groups is that there are eight of them—four D-positive groups (namely, CDE, CD, DE, D) and four D-negative groups (namely, CE, C, E, X), or whatever geneticists of the future may regard as an appropriate terminology—and that anti-C, anti-D, and anti-E agglutinins may be formed by immunisation in those who lack the corresponding agglutinogens?

REACTIONS OF THE CDE ANTISERA

CDE blood-groups	Reactions of antisera			English percentage frequency
	Anti-C	Anti-D	Anti-E	
CDE	+	+	+	13·63
CD	+	+	−	53·40
DE	−	+	+	14·08
D	−	+	−	2·06
CE	+	−	+	0·02
C	+	−	−	0·77
E	−	−	+	0·94
X	−	−	−	15·10

The CDE groups are of less importance clinically than the ABO groups, about which also there is a large and expanding body of information. This information is likewise of great importance and interest to serologists and geneticists, and no-one has cast more light on it than Dr. Wiener, who wrote the classical source-book on the subject: but is it not true that what the general

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1. Sayers, M. A., Sayers, G., Woodbury, L. A. *Endocrinology*, 1948, 42, 379.

nedical public needs to know about the ABO blood-groups s that there are four of them—namely, AB, A, B, O—nd that anti-A and anti-B agglutinins are found in those who lack the corresponding agglutinogens?

Aberdeen and North-East of Scotland Blood
Transfusion Service, Bacteriology Department,
Foresterhill, Aberdeen.
T. M. ALLAN.

CARDIAC CONTUSION

SIR,—Dr. McGill's paper on Cardiac Contusion (May 17) is disturbingly titled. Cases of genuine cardiac contusion are so few that each alleged instance ought to be carefully reviewed; there is too much at stake, especially in the field of industrial hazards and their compensation.

1. The site of injury—the left nipple area—was one in which much of the force of the blow would be radiated, unlike the state where the sternum is struck.

2. The coughing of blood might be associated with heart-failure or, better, with lung and not heart injury. Pulmonary hæmorrhage was described in the necropsy report, although "no evidence of contusion of the lung was seen."

3. The heart was distinctly enlarged (390 g.). In the absence of hypertension and cardiovalvular disturbance, coronary arterial disease is a prominent cause of cardiac hypertrophy.

4. Occlusion is not the only cause of coronary arterial failure. Dilatation of the lumen following loss of mural elastic tissue also is responsible for inefficiency of the coronary circulation.

Dr. McMurray's caution in interpreting the microscopic features of a myocardial section or sections is amply justified.

A good example of true cardiac trauma was recently reported by Pollock et al.[1]

A 21-year-old soldier fell asleep while driving a car, which dropped 30 feet over an embankment. His chest struck the steering-wheel with such violence as to make "a large concave deformity" in the wheel; and he became unconscious. The patient died 2 months later. Necropsy showed evidence of rupture, with scarring, of the interventricular septum.

Department of Pathology,
St. Joseph Hospital,
Fort Wayne, Indiana, U.S.A.
S. M. RABSON.

CEREBRAL AIR EMBOLISM COMPLICATING SPONTANEOUS PNEUMOTHORAX

SIR,—One of the serious accidents during induction of artificial pneumothorax is air embolism. Rarely air may enter the pulmonary veins and pass into the cerebral blood-vessels, resulting in hemiplegia or other forms of paralysis. Spontaneous pneumothorax is very rarely complicated by cerebral air embolism, as it was in the following case.

A Hindu man, aged 25, was admitted to hospital complaining of severe breathlessness and inability to move the left upper and lower limbs in the past twenty-four hours. On the previous morning when he had got up he had felt a sudden sharp pain over the precordium. Shortly afterwards he became suddenly unable to use the left upper and lower extremities, and gradually he became breathless. In the previous year he had had bilateral active pulmonary tuberculosis.

The patient looked acutely ill but was conscious; blood-pressure 100/70 mm. Hg, temperature 98°F, pulse-rate 120 per min., and respirations 60 per min. There were signs of left-sided pneumothorax: the trachea was shifted to the right; the apex-beat was felt in the right 5th intercostal space 2 in. from the mid-sternal line. There was also evidence of left-sided facial paralysis (supranuclear type) with hemiplegia on the same side. A blood-count showed 16,450 white cells per c.mm. (polymorphonuclears 93%, lymphocytes 7%).

Treatment and Progress.—The patient was given stimulants. 700 ml. of air was withdrawn from the left pleural space. The aspirating needle was left in situ with a long piece of rubber tubing leading from the needle to a bowl of water on the floor. The patient's condition improved slightly, but thereafter he passed into deepening coma and died the same night.

Evidently the cerebral air embolism was a complication of the spontaneous pneumothorax. Despite the continuous drainage of air from the pleural cavity, the leakage of air into the cerebral blood-vessels persisted, leading to massive air embolism and death.

My thanks are due to Dr. H. N. Bhatt, F.R.C.S.E., principal of the Medical College, Agra, for his permission to publish this report.

Department of Medicine,
Medical College,
Agra, India.
P. N. LAHA.

REACTION TO PENICILLIN

SIR,—Three of your correspondents have described reactions following an injection of penicillin—Dr. Yuval (Jan. 19), Dr. Smolnikoff (May 17), and Dr. Bell (May 24).

A boy, aged 8, was admitted to the Margate General Hospital on May 19 at about 10.50 A.M. He suffered from chronic bronchitis, and had been having 'Estopen' (penicillin G diethylaminoethyl ester hydriodide) since May 3. He had had 250,000 units on alternate days for two weeks and 250,000 units daily during the third week. On May 19 at 10 A.M., immediately after an intramuscular injection of estopen into the right buttock, he collapsed; there were a few clonic movements of his limbs, he became pale, then cyanosed and pulseless, and his breathing ceased. Artificial respiration was immediately given, and sighing infrequent respirations returned and his colour improved. About 20 min. later he had further clonic movements of his limbs, and he vomited. On reaching hospital he was unconscious, restless, irritable, and slightly cyanosed. He was retching and vomiting small quantities. Breathing was regular and quiet. The pulse-rate was 84, and the beat was regular and of good volume. His pupils were dilated and they reacted to light. The knee-jerks were increased, and the plantar response was flexor on the right and extensor on the left. The limbs were in the flexed position, the muscles of both limbs being spastic.

He was given an injection of soluble phenobarbitone at 11 A.M. The restlessness persisted until 11.45 A.M. and the vomiting until 2 P.M. He remained unconscious. At 7 P.M. he attempted to speak and seemed able to understand, and at 10.20 P.M. he regained full consciousness. He has shown no abnormal signs since.

This condition closely resembled an anaphylactic shock reaction. The patient had never had asthma or hay-fever, or a previous reaction to drugs, and there was no family history of allergy.

Hypersensitivity to penicillin commonly produces skin eruptions or drug fever. Toxicity due to large dosage is very rare as far as intramuscular injections are concerned.

The General Hospital,
Margate.
R. WYLIE-SMITH.

THE ELECTRO-ENCEPHALOGRAM

SIR,—May I, prompted by Dr. Jewesbury's article (May 24), mention the difficulties which we as electro-encephalographers encounter in E.E.G. interpretation? Some of these, I feel, are not readily appreciated by sections of the medical profession.

Mainly, the principal difficulty is in convincing our clinical colleagues that what is represented in the E.E.G. is a graph of cortical *function* and not one of structure. Hill[1] has aptly said:

> "The clinical mistakes in diagnosis, the bewilderment of interested observers, do not arise from any capriciousness upon the part of the brain, but upon our human ignorance and human fallibility. The limitations lie not in the technique but in the electro-encephalographer."

What we, as electro-encephalographers, are called on to do is to suggest and accurately predict, from a brief "still" of cortical activity, the clinical state that will prevail until death, or some less conclusive pathological state, intervenes. This is comparable to being invited to witness a few minutes of a $2^1/_2$-hour performance of a play with complex plot and many seemingly unrelated characters, and then being expected to describe the whole dialogue from prologue to epilogue. Is it any wonder that so often our conclusions are in doubt?

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[1] Pollock, B. E., Markelz, R. A., Shuey, H. E. *Amer. Heart J.* 1952, 43, 273.

[1] Hill, D. *In* Perspectives in Neuropsychiatry. Edited by Dr. Richter. London, 1950; p. 53.

Salford Royal Hospital. E. B. HOYLE.

A METHOD OF VASECTOMY IN PROSTATECTOMY

SIR,—The usual approach for vasectomy in prostatectomy is through separate incisions which divide the skin, superficial fascia of Camper, and Scarpa's fascia on each side, and expose the spermatic cords just below their exit from the external ring.

Last year, when about to carry out this procedure, it occurred to us that the cord was readily accessible from the median subumbilical prostatectomy incision through which a Millin's prostatectomy had just been performed, and that in this way we could avoid additional incisions. We carried out the operation by this route, and we have used it regularly for the last nine months with complete satisfaction. There have been no difficulties or untoward sequelæ.

In the suprapubic region, Scarpa's fascia fuses with the linea alba for some distance above the pubis, and the cord can be reached immediately below the external inguinal ring where it lies lateral to the median prostatectomy incision, covered only by areolar tissue and Scarpa's fascia as the latter turns down to fuse with the linea alba (fig. 1).

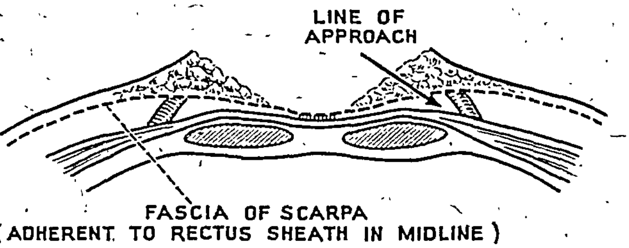

Fig. 1—Diagrammatic section through abdominal wall to show approach to spermatic cord.

The skin at the lower end of the median prostatectomy incision on the right side is raised by a retractor, and an incision is made laterally and subcutaneously through the loose areolar tissue and Scarpa's fascia. The assistant pushes the cord medially, and the operator then hooks up the cord with a pair of curved Spencer Wells forceps or a similar instrument. The vas is then isolated, divided, and ligated (fig. 2). The opening in the fascia is closed with a mattress or a double-loop suture with a single knot. This procedure is repeated on the left side, when the surgeon pushes the cord medially and the assistant hooks it up.

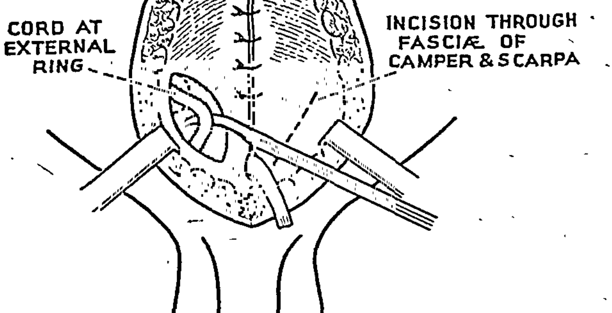

Fig. 2—Exposure of spermatic cord at external inguinal ring.

This simple, convenient, and efficient method not only avoids extra skin incisions, but it obviates any risk of infection from such incisions. The fascial opening seals rapidly after being sutured, so there is little or no risk of infection from the median incision, and the cosmetic result is excellent. The presence of a hernial sac is no contra-indication.

We have since learned that Sarnoff[1] described a similar method for vasectomy in suprapubic cystotomy. It may well be that it is in use elsewhere, but its simplicity and convenience merit further publicity.

J. E. STANLEY LEE

Wolverhampton. HENRY B. YOUNG.

SICKLE-CELL ANOMALY IN GREECE

SIR,—Professor Choremis, whose letter you published on May 24, has in the past made various suggestions about Cooley's anæmia. He has said that the specific bone lesions, described by Cooley as establishing the morbid entity of the disease, were also to be found in secondary anæmias following chronic infections, such as malaria, syphilis, and kala-azar. He confused the ring-shaped red cells with the ring form of *Plasmodium falciparum*, and argued that malaria was the main cause of the disease.[2] He disagreed with me when, in 1936, I suggested that decreased fragility was a hereditary specific element in the disease; but this was later confirmed in Italy and America.

He then found the sickle-cell anomaly in 15% of the inhabitants of Petromagoula—where the malaria-rate is high.[3] But he will find, as I have done, that the proportion is much the same in other areas of Greece, whether malarial or not.

Between 1938 and 1941 Dr. I. Roumanis and I examined most of the patients with chronic anæmia in Petromagoula and the near-by village of Scripou. We found that there was no difference between the incidence of the disease in these two places and other areas in Greece. Moreover, several patients had the typical mongoloid facies of Cooley's anæmia.

Professor Choremis says that sickle-cell anæmia is practically non-existent in Athens; but my latest work enables me to add another 13 Athenian families to the 18 given in my article of April 5. He also states that Cooley's anæmia is rare among Turks; but Frank[4] reported "all forms from classical Cooley disease to thalassæmia minima."

It can be easily established that Cooley's anæmia is associated with certain racial groups—e.g., Alpine, Illyrodinaric, and Armenoid—characterised by mongoloid features (brachycephaly, slant eyes, curved nose, prominent cheek bones, and steep occiput). These groups now prevail in Greece, but another group with Mediterranean characteristics (straight eyes, dolichocephaly), now in the minority, shows no evidence of the disease.

If Professor Choremis will pursue his examinations further he will find a substantially higher percentage of carriers of the sickle-cell trait. He has admitted that he failed to find it in the parents of children who were *positive*, as well as in patients diagnosed clinically, and that his failure was probably due to defective technique.[5] The reason was, I think, that he only constricted the patients' fingers for one minute, and that he disregarded the long negative phase which can occur.

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1. Sarnoff, J. *Med. Times, N.Y.* 1931, 59, 328.
2. Choremis, C., Spiliopoulos, G. *Iatr. Chron.* February, 1936, p. 83.
3. Choremis, C., Zervos, N., Constantinides, V., Zannos, L. Sclavounou, S. *Hellen. Iatr.* 1951, 20, no. 12.
4. Frank, E. *Blood,* 1951, 6, 862.
5. Choremis, C., Zervos, N., Constantinides, V., Zannos, L. *Lancet,* 1951, i, 1147.

It is quite possible to see sickle cells in dry smears. They are clearly shown scattered among the target cells in fig. 3 of my article, and less abundantly in fig. 4. I have known people in whom sickle cells have been seen in dry smears when the trait was not being sought, but who were later proved to be carriers.

Athens. J. Caminopetros.

SICKLE-CELL TRAIT IN AN ARAB

Sir,—In the course of a survey of the sickle-cell trait in Israel various communities have been examined. The finding of this trait among Yemenite Jews and members of other oriental Jewish groups (Iraq, Kurdistan, &c.) has been previously reported.[1, 2]

118 Arabs of both sexes and all age-groups were recently examined. Of this group 98 were bedouins from the Northern Negev (Southern Israel); the other 20 came from various other localities within the former boundaries of Palestine. The bedouins belong to three different tribes from places near the town of Beersheba. A few of these nomadic Arabs present negroid features; most of them do not.

The moist-stasis of Scriver and Waugh[3] was used, and three preparations taken from each person.

No instance of sickling was found among the bedouins; but one Arab, hailing from a village near the town of Ramath Gan (Israel), was found to show sickle cells. He was re-examined on three occasions, and all the preparations were positive each time.

This carrier of the sickle-cell trait is 30 years old, apparently has no Negro ancestry, and certainly has no Negroid features. He is healthy and has neither history nor clinical or laboratory signs of sickle-cell *anæmia*.

In contrast to the Jews so far found positive,[1, 2] his red cells also sickled when examined with 2% ascorbic acid. Stained sickle-cell smears were obtained in the following way: 4 ml. of citrated blood was mixed with 2 ml. of a 5% solution of ascorbic acid; the mixture was incubated for about half an hour and then fixed with a 10% formalin solution in equal parts. The smears were stained with Giemsa solution.

The only instances of sickling observed so far in Arabs have been one in the Sudan,[4] one in Egypt[5] (the patient apparently had Negroid features), and one in Israel.[6]

We express our appreciation and thanks to the Research Council of Israel, which provided a grant for this work; to Alisah Moshe for technical help; and to Dr. H. Kozlovsky and Dr. E. Lehmann for their coöperation.

Hebrew University—Hadassah Medical School, Jerusalem, Israel.

F. Dreyfuss
M. Benyesch.

POTASSIUM IODIDE IN COUGH MIXTURES

Sir,—Your annotation of May 10 describes potassium iodide as a "virtually useless" expectorant and states that the experimental evidence to the contrary is misleading. In the interest of the large number of chronic bronchitics in this country your statement must not remain unchallenged. It is true that the official mixtures (mist. pot. iod. ammoniata, mist. stramon. et pot. iod., mist. lobel. et stramon. co.) all contain only gr. $2^{1}/_{2}$–3 of potassium iodide; even the doses used by Alstead[7] supporting his negative results were small (gr. 5–10).

Gordonoff[8] showed that potassium iodide is a strongly secretolytic substance. In view of this, one should not form a judgment without first having tried a much wider range of dosage than Alstead used. You are wrong in saying that "very large doses, if translated into clinical practice, would be emetic." We usually give patients gr. 15 three times a day and often as much as gr. 20–25. Most of them can take these amounts without any trouble, though they do not necessarily regard their medicine as their favourite drink. Patients whose viscous secretions cause them interminable and exhausting attacks of coughing regard the drug in these doses as invaluable. It liquefies the mucus and thus permits expectoration. Cough and sputum disappear completely in some cases, particularly those in which bronchial infection has not been present for long. If potassium iodide is given continuously, tolerance quickly develops. We therefore give the substance for 3 or 4 consecutive days with a pause of 3 days before starting again. It is interesting to note that the first sign of relief usually appears on the 2nd day of medication. Conversely, at the end of the 2nd or on the 3rd day of the interval the patient often notices the return of his former viscous type of sputum. Surprisingly, cases of iodism have been extremely rare.

Potassium iodide is also very effective in chronic asthma after acute bouts, when the patient feels that he has "phlegm on the chest" but cannot get rid of it. We have seen many cases of intractable "adrenaline-resistant" status asthmaticus in which adrenaline (or isoprenaline) could not widen the bronchi sufficiently to permit the viscous mucus to be coughed up. Potassium iodide very soon "restored" the adrenaline response.

Of course, we do not claim to have made this discovery—there must be many who have had the same experience before us. We are glad that you mention, although somewhat sceptically, the expectorant action of carbon dioxide. We have found it very effective indeed, but its application in general practice is difficult.

University College Hospital, London, W.C.1

H. Herxheimer
Monica K. McAllen.

ROUTINE ESTIMATION OF DINITRO-*ORTHO*-CRESOL IN BLOOD

Sir,—We should like to point out that our recommendations for the prevention of acute poisoning by dinitro-*ortho*-cresol (D.N.O.C.), published in your issue of April 19,[1] are based on correlation of physiological effects with blood-D.N.O.C. levels estimated on whole blood. All the estimations in the experiments and field survey reported from the Department for Research in Industrial Medicine were carried out on whole blood by adaptation of the method described by Parker[2] for the estimation of D.N.O.C. in serum; more than 90% recoveries of D.N.O.C. added to whole blood may be obtained by this technique.

There are at least two disadvantages of using serum instead of whole blood for routine D.N.O.C. estimations. The first is that venepuncture is necessary to obtain large enough samples of blood (1–2 grammes) whereas Harvey[3] has described a modification of Parker's technique by which D.N.O.C. can be estimated accurately in 0·1–0·2 g. whole blood obtained from finger-tip or ear-lobe puncture. Secondly, since it is known that D.N.O.C. in the blood is bound to the serum-albumin, relatively little being held by the cells, the serum-D.N.O.C. concentration will vary in different individuals depending upon the packed-cell volume. When hæmoconcentration is present, wide variations will occur, and the serum-D.N.O.C. level may bear little relation to the physiological effects.

Bruce and Mackay[4] have suggested that Harvey's modification of Parker's technique may be of a limited application where a considerable number of specimens is received by post at the central laboratory. In our experience samples of whole blood amounting to 0·1–0·5 g.

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[1] Dreyfuss, F., Benyesch, M. *Nature, Lond.* 1951, 167, 950.
[2] Dreyfuss, F., Mundel, G., Benyesch, M. *Harefuah*, 1951, 41, 168.
[3] Scriver, J. B., Waugh, T. R. *Canad. med. Ass. J.* 1930, 23, 375.
[4] Daland, G. A., Castle, W. B. *J. Lab. clin. Med.* 1948, 33, 1082.
[5] Abbasy, A. S. *Blood*, 1951, 6, 555.
[6] Heichmann, J., and Salomon. Personal communication.
[7] Alstead, S. *Lancet*, 1939, ii, 932.
[8] Gordonoff, T., Lehmann, S. *Z. exp. med.* 1936, 99, 731; *Ergebn. Physiol.* 1938, 40, 53.

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[1] Bidstrup, P. Lesley, Bonnell, J. A. L., Harvey, D. G. *Lancet*, April, 19, 1952, p. 794.
[2] Parker, V. H. *Analyst*, 1949, 74, 646.
[3] Harvey, D. G. *Lancet*, April 19, 1952, p. 796.
[4] Bruce, J., Mackay, R. *Ibid*, May 31, 1951, p. 1115.

can be sent by post in glass-stoppered tubes of standard size and the extraction carried out without transferring the blood to another tube. Further, we would emphasise that the photoelectric absorptiometer described by Harvey[3] does not represent anything new but is a modification of the well-known single-cell absorptiometer which may be built up at little cost in a routine laboratory where a suitable commercial piece of apparatus may not be available. We agree with Bruce and Mackay[4] that the Spekker may be employed to estimate small quantities of D.N.O.C.; and by using a standard cell of approximate capacity 0·9 ml. we have obtained excellent recoveries of 5 µg. of D.N.O.C. per g. of blood in 0·1 g. quantities of blood by using 2 ml. of ketone.

Department for Research
in Industrial Medicine,
London Hospital, E.1.

D. **GRAHAM HARVEY**
P. **LESLEY BIDSTRUP**.

VASOSPASM AFTER REMOVAL OF PROLAPSED INTERVERTEBRAL DISC

SIR,—Reports on the results of operations for prolapsed intervertebral disc rarely refer to vascular symptoms attributable to sympathetic overactivity.

Falconer et al.,[1] in a review of 100 cases, describe one in which operation was followed by burning pain in the leg; they regarded this as causalgic.

The patient had had a bone-graft following removal of a prolapsed disc. When the wound was re-explored, the first sacral root was found to have been penetrated by a fragment of bone used for the fusion. Removal of the fragment resulted in only temporary relief of pain. Subsequent cordotomy abolished the pain.

The same workers refer to a second case of causalgic pain after a "straightforward" disc operation; in this case the pain was only partly relieved by cordotomy. They also cite Freeman and Watts[2] as having had a case which was treated by prefrontal leucotomy.

Wertheimer et al.,[3] reviewing 175 such operations, mention 2 cases with postoperative symptoms which they concluded were of vascular origin, and which were relieved by procaine block of the lumbar sympathetic.

In the following case vasospastic phenomena appeared in one lower limb after complete relief of sciatica by removal of a prolapsed disc. This condition was successfully treated by lumbar sympathectomy.

A woman, aged 40, was seen at Edgware General Hospital on June 8, 1948, when she complained of right-sided sciatica of 2$^1/_2$ years' duration. The lumbar curve was flattened. Forward bending and straight-leg raising were limited by pain. Both ankle-jerks were present. Radiographic examination showed a diminished space between the 4th and 5th lumbar vertebræ. Prolapsed disc with irritation of the nerve-root was diagnosed. Physiotherapy was prescribed, and a lumbosacral belt was fitted.

The patient returned on Feb. 22, 1949, and said that after a fall down some steps she had had a severe exacerbation of her sciatica.

First Operation.—On March 10, 1949, the 4th lumbar space was explored. The disc was found to be bulging posteriorly. The overlying nerve-root was notably short, tight, and adherent and offered considerable resistance to the retraction necessary for adequate exposure of the prolapsed disc. The annulus fibrosus was incised and the nucleus was removed by curettage.

Postoperatively the patient was free from sciatic pain. She complained, however, of numbness in the right leg. Convalescence was complicated by paresis of the peronei and anterior tibial muscles, which made walking difficult. This rapidly improved and had practically disappeared at the time of discharge from hospital 25 days after operation. 6 weeks later the patient had no symptoms and walked normally.

On Aug. 7, 1951, 2 years and 5 months after operation, the patient returned complaining of intense coldness of the right foot, which also felt numb, and of cramp in the thigh. These symptoms were worse in cold weather and she dreaded the approach of winter. She had had no return of sciatica. She could now bend forward and touch the floor without pain, and she had a normal range of painless straight-leg raising. Dorsiflexion of the ankle was as strong on the right side as on the left. The right leg and foot were cold to the touch and were purplish-red. There was no ulceration. The peripheral pulses were all palpable. There was no muscle-wasting and no loss of sensation. Stroking the skin caused a tingling sensation.

A right paravertebral sympathetic block was performed with procaine. In 20 minutes the temperature between the toes rose 19°F. The patient enthusiastically described the welcome feeling of comfort in the limb when it warmed up. This lasted for several days.

Second Operation.—On Oct. 23, 1951, right lumbar sympathectomy was performed. The result of this operation fully justified expectations. The limb has since been hot, objectively and subjectively, and the numbness and cramps have been completely relieved. 4 months after operation the patient said that she had stood the rigors of the winter without any troubles, and that she felt better than ever before.

Trauma to the nerve-root, incidental to exposure of the prolapsed disc, clearly caused the transient paresis and numbness that followed the first operation. Subsequent fibrosis in and around the nerve-root probably excited the vasoconstriction which caused the intense coldness of the foot 2 years after that operation. In this case the clinical picture was one of pure vasomotor disturbance and provided a clear indication for sympathetic denervation.

It is likely that in some cases of similar damage to the nerve-root vasoconstrictive symptoms are mingled with those of a segmental character. The elimination of the former by procaine sympathetic block would be a useful step in assessing the possible need for re-exploration of the nerve-root.

Edgware General Hospital.

FRANK FORTY.

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1. Falconer, M. A., McGeorge, M., Begg, A. C. *Brit. J. Surg.* 1948, 35, 225.
2. Freeman, W., Watts, J. W. *Lancet*, 1946, i, 953.
3. Wertheimer, P., Mansuy, L., Bourret, J., Gautier, R. *Lyon chir.* 1949, 44, 240.

OUR CRIME-SHEET

SIR,—In your important and alarming leader last week on this subject, you quote Sir Sydney Smith's statements that "criminals are to a great extent developed in the nursery," and that the value of discipline is being too much disregarded.

As one who works with mothers and children in welfare centres I feel that, although laziness and lack of parental moral codes may play their part in the development of the juvenile criminal, in many cases the fault is in the parents' misguided ideas of child upbringing. They feel, many of them, that discipline is wrong and harmful to the child—that it "breaks his spirit"—and they are unable to see that a child who has his every wish granted, and who is allowed to disrupt the family circle with his likes and dislikes, will have great difficulty in taking his normal place in the larger social unit when he grows up. He is accustomed to being a focal point with few responsibilities towards the well-being of the community.

You ask who is to train the parent. One answer lies in the work of the welfare clinics where we have the time to deal with, and a unique opportunity for spotting the first signs of, antisocial behaviour. It is in the very earliest stages that the parents require advice, as once true maladjustment has developed the whole problem is much more difficult; and often school does little to help, as the modern trend is to regard discipline during school hours as repressive rather than educational.

One other important social problem is tied up with all this. Where a mother has to spend her time dealing with ill-disciplined children, her relationship with her and may suffer and major family breakdowns result, with the attendant effect on juvenile nquency.

believe it is of the utmost importance to help parents ealise that kindly discipline rather than laissez-faire he answer when the very first sign of the won't won't play, won't sleep phase shows itself. A le child, home, and community will only come where child learns to take its place as a coöperative member he family from the earliest age.

would suggest that even greater efforts must be le in the welfares centres, by antenatal talks, &c., ielp with the mental as well as the physical health he child.

anmore, Middlesex. AUDREY STEVENSON.

SYNERGY OF HEALTH AND EDUCATION

IR.—I read with interest your leading article of r 10.

great number of maladjusted children are referred hild-guidance clinics by school medical officers; and m impressed by the skilful way in which these s are selected. The school doctor's intimate knowge of the circumstances in the schools is invaluable. forms a very important link between the school and child-guidance clinic.

CHILD PSYCHIATRIST.

Births, Marriages, and Deaths

BIRTHS

FTON.—On May 29, at the Royal Infirmary, Edinburgh, to Eileen, wife of Prof. John Crofton—a daughter.

BY.—On May 30, at Queen Charlotte's Hospital, London, to Dr. Muriel Dalby (née Carr), wife of Lieutenant J. E. Dalby, R.A.M.C.—a son.

OOP.—On June 1, to Joan, wife of Dr. R. C. Droop—a daughter.

AN-JONES.—On June 2, to Maureen (née Bartholomew) and Mr. David Elgan-Jones, F.R.C.S., 52, Belsize Park, N.W.3—a daughter.

GH.—On June 3, at 61, The Drive, Hove, to Nancy (née Utton), wife of Dr. K. M. Gough—a daughter.

LDANE.—On June 1, to Vanora (née McWilliam), wife of Dr. J. H. Haldane, of Netherton, Dudley, Worcs—a daughter.

VONS.—On May 28, to Mary Patricia, wife of Dr. Peter M. Jeavons, of 160, Hagley Road, Birmingham—a son.

LIFFE.—On May 31, at Plateau Hospital, Jos, Nigeria, to Jillian (née Fletcher) and Dr. Robin S. Jelliffe—a son.

MILT.—On June 8, at Salisbury General Hospital, Wiltshire, to Janet (née Brownscombe), the wife of Mr. Philip Shemilt, F.R.C.S.—a daughter (Jane).

YLOR.—On May 30, at Harlow, Essex, to Joy (née Robertson), wife of Dr. Charles Taylor—a son.

YLOR.—On May 22, at Gloucester, to Phyllis (née Plumbridge), wife of Dr. W. K. Taylor of Godalming, Surrey—a daughter.

LBON.—On May 31, at Glebe House, Baylham, near Ipswich, to Mary, wife of Dr. J. W. S. Welbon—a daughter.

ITFIELD.—On May 26, at Churt Wynde, Hindhead, to Pauline (née Howe), wife of Dr. P. G. Whitfield—a daughter.

MARRIAGES

PEWELL-ASH—ASH.—On May 12, at Blandford Forum, Dorset, Edwin Lancelot Hopewell-Ash, M.D., to Christine Ash (née Diamandis).

MB—GREENWAY.—On May 22, at St. Margaret's Church, Rottingdean, Sussex, John Tunstall Lamb, M.B., to Diana Joy Greenway.

DEATHS

DREWS.—On May 29, at Lancaster, Mary Neville Andrews, M.D. Lond., formerly medical missionary in China and the Henry Lester Institute, Shanghai.

HTON.—On June 3, at Bronwylfa, Machynlleth, John Caradoc Ashton, M.B. Edin., aged 78.

LL.—On June 5, at West Malling, Kent, Thomas Paterson Gill, M.B. Aberd., F.R.C.S.E., D.L.O., aged 51.

ETTY.—On May 30, at Kettering, Harold Cooper Pretty, M.R.C.S.

ILLES.—On June 2, Charles Fitzgerald Willes, M.R.C.S., surgeon lieut.-commander, R.N. retd., of Abbots Leigh, near Bristol.

CORRIGENDUM: *Discovery of Anaphylaxis.*—In our account lay 31, p. 1121) of the commemoration in Paris of the 50th niversary of this discovery, we said that Sir Henry Dale, M., spoke on the Mechanism of Anaphylaxis. He was in ct not present, and Dr. Halpern gave a resumé of a paper Sir Henry on this subject.

Public Health

An Outbreak of Trichiniasis

BETWEEN April 28 and May 4 over 20 people in Barry, Glamorganshire, sought advice for headache, swelling of the face, and muscular pains. Most of them gave a history of gastro-intestinal symptoms during the previous fortnight, and they had all eaten sausages or sausage meat—much of it undercooked—during the first fortnight in April. There was a definite increase in the eosinophil-count in every case. Biopsy was performed on two patients, and larvæ of *Trichinella spiralis* were found in both. A feature of the outbreak was the chronicity of symptoms, but all the patients are now recovering.

A consignment of pork which was distributed to sausage makers in the town in early April did not come from the usual supplier for the area. Further investigations are being made.

We are indebted to Dr. Mary Lennox, medical officer of health for Barry, for this information about the outbreak.

Paratyphoid B on the Welsh Border

Up to and including the week ended May 31, 90 cases of paratyphoid B infection had been notified from the districts of Monmouthshire and Glamorganshire involved in the outbreak mentioned in our issue of May 24 (p. 1073). The majority of cases come from Gelligaer (34), Bedwellty (15), Mynyddislwyn (15), and Pontypridd (7). Dr. A. G. M. Severn, medical officer of health for Pontypridd, who has kindly told us about the cases in his area, thinks that the outbreak now shows more of the characteristics of a milk-borne infection in its age and sex distribution. Certain milk-supplies are under suspicion, and on May 22 he advised the people of Pontypridd to boil all milk. A number of patients visited the same café in the town, but this may only be involved because it draws its milk from the same source as the homes of several patients. The investigations are continuing in all districts.

Cancer Registration in England and Wales

In 1950 the General Register Office published a booklet on Cancer Registration in England and Wales.[1] Supplementary tables,[2] now issued, give the corrected survival and recovery rates at the first and second anniversaries, *and provisional rates at the third anniversary, of treat*ment for cases of primary cancer registered during 1945 and 1946, at the more important sites.

Infectious Diseases in England and Wales

Disease	Week ended May				
	3	10	17	24	31*
Diphtheria	21	16	27	25	24
Dysentery	241	367	328	269	276
Encephalitis:					
Infective	3	4	4	2	2
Postinfectious	3	1	..	..	1
Food-poisoning	95	91	134	127	137
Measles, excluding rubella ..	4743	4494	5749	6246	6616
Meningococcal infection	39	40	43	42	31
Ophthalmia neonatorum	36	36	36	44	39
Paratyphoid fever	10	5	22	53	45
Pneumonia, primary or influenzal	582	491	433	430	380
Poliomyelitis:					
Paralytic	15	15	25	18	26
Non-paralytic	9	6	12	19	18
Puerperal pyrexia and fever ..	254	267	245	255	225
Scarlet fever..	877	1033	1088	972	915
Smallpox	..	..	..	..	..
Typhoid fever	5	3	1	1	3
Whooping-cough	3116	2993	2905	2785	2595

* Not including late returns.

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1. Studies on Medical and Population Subjects, no. 3. H.M. Stationery Office, 1950; see *Lancet*, 1950, ii, 532.
2. Studies on Medical and Population Subjects, suppl. no. 3. Cancer Registration in England and Wales: Third Year Recovery and Survival Rates. H.M. Stationery Office. Pp. 27. 1s. 3d.

Notes and News

SAVING BEDS AT CAMBRIDGE

IN August, 1949, to eke out its beds, Addenbrooke's Hospital started a home-care service. The venture has proved popular, and last year 166 patients were looked after in their own homes by their own family doctor, and, with the help of the district nurse, cared for by their own relatives. Domestic help is provided free for the first fortnight where necessary. The saving in beds has been real. The Department of Human Ecology has analysed the length of stay in hospital of patients with appendicitis and its report shows that under the home care scheme in 1950 5·61 bed-days per male patient and 4·67 bed-days per woman patient were saved.

During 1951, 168 patients were recommended for home care and of these 30 were *not accepted*—25 because their home conditions were unsuitable, and 3 because their relatives were unwilling to take them. Of the 138 patients who were accepted, 9 came from medical wards, 120 from surgical wards, and 6 were awaiting admission to chronic-sick wards. There are roughly about 30 patients receiving home care at a time, and during 1951 8866 days of home care were given. Much of the success of the scheme has been due to the willing help given by 107 general practitioners. Their support has been the more readily won because they know that readmission of patients to hospital is guaranteed, and 6 patients were in fact readmitted during 1951. Most of the patients said they preferred being nursed at home, and some, especially the younger ones, confessed to being depressed by the presence in the ward of people who were seriously ill.

"METABOLISM"

As the medical sciences become further and further subdivided new journals come into existence to give expression to new specialties. But there is also a tendency in the reverse direction, for fresh discoveries and techniques often overlap from one branch of science to another. This tendency towards reintegration lies behind the publication of the latest American journal—*Metabolism, Clinical and Experimental*[1]—and is well exemplified by an article in the first number, in which J. Meites discusses the nutritional requirements of the body at varying levels of hormonal function. His experiments concern the interaction of thyroid and adrenal hormones with vitamin B_{12} and antibiotics such as penicillin and aureomycin, and cut across the boundaries of endocrinology, microbiology, and the science of nutrition. The new journal is clearly a fitting vehicle for the publication of articles such as this. Yet it might be objected that its title is altogether too wide. Metabolism is a concept which runs through all the medical sciences, and anyone wanting to track down an article in almost any branch may find he has to include *Metabolism* in his search. But the prospect of inconvenience should not prevent us from welcoming this new venture for its refreshingly anti-specialist bias. The high standing of the editorial board (headed by Dr. Samuel Soskin, with Dr. Fuller Albright as consulting editor) inspires confidence. The first number does not announce any major discovery, but most of the articles attain the high standard we have come to expect from the best American journals. Valuable abstracts and book reviews are also included.

THE CHILD AND HIS LUNGS

"HAVE you done your exercises?" that curiously useless inquiry, is made daily by parents who have very little hope of an affirmative reply, whether the exercises are designed to arch flat feet, expand an asthmatic chest, or further the art of piano-playing. Very few children, left to themselves, will do any kind of exercises regularly, not being convinced, at that age, that their health or virtuosity are the most important things in the world. Piano-playing must be left to the experts in that field, but parents who want health exercises done must be willing to join in, anyhow to the extent of making them interesting.

Dr. G. F. Walker, two years ago, published a set of ten exercises for the asthmatic child, and has just produced a new edition.[2] The exercises, preceded by a useful little homily on the general management of asthma, are shown in photographs, the performer being a sensible-looking girl of about twelve. The asthmatic child will find them easy to follow; and with the book before him, a parent to give the commands in the manner of a gym instructor, and perhaps a gramophone record to supply rhythm and interest, he may well be brought to do his exercises regularly, to his great physical benefit. The movements chosen are designed to develop and strengthen the muscles of the chest wall, get the shoulders in proper alignment, and keep the child's gait and posture in good order.

For younger children with bronchiectasis Guy's Hospital have printed a useful folder on postural drainage.[3] A short preamble for parents is followed by a set of clear drawings and a running commentary in larger type which the child can read and understand for himself. The first page cleverly makes plain the principle of postural drainage by showing honey running stickily out of a tilted jar. The middle pages illustrate the advantages of a hot drink before the tilted posture is assumed, and also the way of putting drops into the nose. The back of the card shows the way different parts of the lungs can be drained, with the help of a raised foot to the bed, or a frame to hump the mattress. The very nice drawings will make the doctor's intentions clear to the child, which of course is half the battle; but the parent must be at hand with the hot drink and the necessary encouragement if the directions are to be carried out regularly.

INTERNATIONAL SANITARY REGULATIONS

THE World Health Organisation has completed the task of revising the international sanitary conventions, and has combined them in one volume which has now been published as the *International Sanitary Regulations*.[4] The regulations provide for the world-wide control of the "quarantinable diseases"—plague, cholera, yellow fever, smallpox, typhus, and relapsing fever. The first part of the book includes the debates of the special committee which drafted the regulations, and the resolutions on international quarantine passed by the fourth World Health Assembly. The assembly considered that the regulations should be only the first of a series of measures to check the spread of epidemic diseases. The second part contains the text of the regulations and an explanatory memorandum. The principle that has guided the committee is that the maximum security against the introduction of disease should be achieved with the minimum of interference in international traffic. An efficient public-health service is more effective than a barrier of quarantine measures.

A NEW SPANISH JOURNAL

THE first number of *Revista de Diagnostico Biologico* appeared in February. It is the official organ of the Asociacion Nacional de Medicos Especialistas de Analisis Clinicos de Espana, which body is affiliated to the International Society of Clinical Pathology. Contributors to the first issue include Dr. Antonio Utrilla (excretion of 17-ketosteroids in certain skin diseases of possible endocrine origin), Prof. J. Sanz Ibanez (histopathology of injuries caused by the atom bomb), Prof. F. Mas y Magro (experimental eosinophilia), and Dr. T. H. Ham, Dr. W. B. Castle, Dr. F. H. Gardner, and Dr. Geneva A. Daland (review of the laboratory diagnosis of polycythæmia and anæmia). The number includes also a review of recent articles and books, a section devoted to professional matters, and a foreword by Dr. A. Utrilla Dominguez, president of the Spanish society and director of the scientific council of the journal. The editor is Dr. S. Larregla Nogueras.

University of Cambridge

Sir Lionel Whitby has been appointed vice-chancellor for a second year.

Royal College of Physicians of Ireland

On June 6 Dr. J. F. Docherty was admitted to the fellowship, and Dr. Sarah L. Campbell and Dr. O. C. Ward to the membership.

Orthopædic Congress

A joint meeting of the orthopædic associations of America, Canada, Australia, New Zealand, South Africa, and Great Britain is to be held in London from June 30 to July 4.

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[1] Published bimonthly by Grune & Stratton, New York. Obtainable in Britain from Baillière, Tindall, & Cox, 7, Henrietta Street, Covent Garden, London, W.C.2. Annual subscription £4.

[2] The Asthmatic Child. The prevention of asthma by simple home methods. Bristol: John Wright & Sons. London: Simpkin Marshall. 1952. Pp. 19. 2*s.* 6*d.*

[3] Postural Drainage of the Lungs. Department of Medical Illustration, Guy's Hospital Medical School, London, S.E.1. Cards 6*d.* each, 22*s.* for 50, £2 for 100, and £17 for 1000, post free.

[4] *Off. Rec. World Hlth Org.* 1952, no. 37. *Obtainable from* H.M. Stationery Office, P.O. Box 569, London, S.E.1. Pp. 443. 16*s.* 3*d.*

London Medico-Chirurgical Society

The annual banquet of the society will be held on Tuesday, July 8, at the Drapers' Hall, Throgmorton Avenue, E.C.2, at 8 P.M.

Isonicotinic Acid Derivatives Released in U.S.A.

The United States Food and Drug Administration has released isonicotinic acid hydrazide and its isopropyl derivative "for use under close medical supervision" (*New York Times*, June 5). These drugs, now grouped in the U.S.A. under the general term "isoniazid," have given promising result in the treatment of tuberculosis (see *Lancet*, April 5, 1952, p. 702). The Food and Drug Administration recommends that their application should be restricted to patients who are not responding satisfactorily to streptomycin therapy. The label on the manufacturers' packages will state: "For use in the treatment of streptomycin-resistant tuberculosis under close supervision of a physician." The Food and Drug Administration also states: "There is growing concern about the possible effects of promiscuous and indiscriminate use. There have been reports of resistant strains of tubercle bacilli after varying periods of treatment. For this reason the F.D.A. medical men feel the drug should be used in selected cases where it may be a life-prolonging or life-saving measure."

Symposium on Deprived Children

During the past two years, the International Children's Centre has arranged a number of symposia and specialist courses in European countries, and from June 9 to 18 it is holding in London a Symposium on Deprived Children. The meeting, which has been organised in collaboration with the British Council, the Home Office, and the Ministry of Health, is being attended by delegates from the United States and from 15 European countries. The chair is being taken by Mrs. Alva Myrdal, director of the social sciences department of UNESCO.

In Memory of William Hunter

The London County Council have erected a plaque on the Lyric Theatre, Great Windmill Street, to commemorate the site of Dr. William Hunter's house and dissecting-theatre. On June 7 this was unveiled by Miss Dorothea Oliver, a great-great-great-niece of William Hunter. Dr. T. B. Jobson, of Guildford, a great-great-great-nephew, was also present. Sir Arthur Porritt, president of the Hunterian Society, presided over the ceremony, and others who attended were Dame Hilda Lloyd, P.R.C.O.G., Sir Wilson Jameson, senior warden of the Society of Apothecaries, Lord Webb-Johnson, president of the Royal Society of Medicine, Sir Gordon Gordon-Taylor, and Dr. J. A. Scott, medical officer of health for the County of London. An exhibition illustrating Hunter's work, life, and interests will be open at the Iveagh Bequest, Kenwood, from June 11 to the end of August.

Medical Sickness Society

Presiding at the annual general meeting of the Medical Sickness, Annuity, and Life Assurance Society on June 3, Mr. R. J. McNeill Love said that the 1946 rate of bonus on the Sickness Fund would be maintained, or in some cases raised; but the position of the life-assurance fund was not so favourable, and in the interests of members holding with-profit life-assurance policies it had been felt advisable not to declare a bonus in respect of the past five years. The measures taken by the Government to exercise monetary control and the consequent fall in the prices of Government securities, affected the life-assurance fund particularly. The fall in value was largely theoretical so far as the society was concerned, because the bulk of the securities affected were redeemable at a fixed date; but valuation must be made on the basis of present conditions, and it was decided generally to write down to current market prices. This would enable the society to face the future with confidence, and as an indication of that confidence the board was recommending the payment of an increased rate of interim bonus in respect of claims arising during 1952. Mr. McNeill Love went on to say that doctors had found 1951, on the whole, a difficult year, as was attested by a certain fall in the amount of new life assurance taken out; but the Danckwerts adjudication should enable general practitioners at any rate to set aside larger sums by way of premiums. About a quarter of the total number of male doctors between ages 35 and 64 held immediate sickness and accident benefit with the society, and the total membership was now 13,429, an increase of 672 during the year.

Wiltshire Research Scholarship

Applications are invited from registered medical practitioners for this scholarship which carries an honorarium of £400 per annum. Its object is to encourage research in cardiology by offering an opportunity for study and travel abroad. Inquiries should be addressed to the dean, King's College Hospital Medical School, Denmark Hill, London, S.E.5.

British Cardiac Society

The annual general meeting of the British Cardiac Society was held this year in Sheffield on May 29 under the chairmanship of Dr. J. W. Brown. The programme, which was arranged by Dr. Samuel Oram, the secretary, included papers on pulmonary artery and pulmonary capillary pressures in mitral stenosis and their response to exercise, the œsophageal pulse in the diagnosis of mitral incompetence, valvulotomy in congenital mitral stenosis, the anatomy of pulmonary stenosis, rapid methods of assessing heart-failure, and the heparin-retarded coagulation-time in coronary occlusion. Prof. J. McMichael showed a film on Cardiac Output in Man and Dr. Paul Wood one on the Clinical Value of the A Wave of the Jugular Pulse.

Anglo-French Exchange Bursaries

The following have been awarded bursaries for special studies in France under the exchange scheme which the French Embassy in London has arranged between the Institut National d'Hygiène in Paris and the Ciba Foundation, London:

G. W. D. HENDERSON, consultant pathologist, deputy director of Salisbury area pathological service.

K. W. LO[illegible] [illegible] to the thoracic unit, The Hospital for Sick Children, Great Ormond Street, London.

F. W. NASH, research fellow in pediatrics, Philadelphia Children's Hospital, U.S.A.

J. F. SKONE, Elliston scholar, London School of Hygiene and Tropical Medicine.

E. A. WRIGHT, junior lecturer in pathology, Guy's Hospital, London.

Westminster Hospital

The old students' dinner of this hospital was held in London on June 6 with Dr. Andrew Shinnie, medical officer of health for Westminster, in the chair. Sir Adolphe Abrahams spoke of the precarious state of the medical school when he joined it: the audience at his first lecture seems to have consisted of a single student. But dissolution or absorption was impossible, he said, for a school with such teachers as Arthur Evans and Rock Carling; and in due course the staff came to include men from almost every school in London, not to mention the Antipodes. The trickle of prospective students became a stream and then a torrent. The aim was to establish a small but very select school; though he did not go so far as the dean who thought 15 students the most suitable number—15 rugger blues. A medical school, it had been stated, could be judged by three criteria—the staff, the students, and the hospital journal. He need not speak of the Westminster staff, but the students were the best in London, which meant the best in Britain, which meant the best in the world. A hospital journal always attracted infinite criticism and precious little approbation: people expected it to have the combined merits of the *British Medical Journal*, *Lancet*, *Practitioner*, *Punch*, the fourth leader of the *Times*, and *Men Only*; but at least the Westminster magazine challenged comparison with any other. Surveying Westminster today, he saw a fine new hospital with an eminent staff enhancing its fame; a never-ceasing stream of newly qualified practitioners who were a credit to Westminster and to medicine; a fine new athletics ground; and a table groaning under the weight of trophies. Sir Stanford Cade, in proposing The (many and distinguished) Guests, said that it was up to the younger generation to make the second Elizabethan era as sparkling as the first. He recalled his days as a midder boy in the slums of Westminster, when he had to send for the fire-brigade because his patient had postpartum hæmorrhage and there was no way of getting her out of the house except through the window. The City of Westminster could, he thought, take pride in the vast changes made since those days. After Mr. H. F. C. Crookshank, the Lord Privy Seal, had responded gratefully for the guests, Mr. R. S. Taylor proposed The Chairman. Dr. Shinnie, in reply, said that he had been connected with the hospital for 35 years and a teacher in the medical school for 25. Public health had travelled a long way since those days, and he was proud of the association between the city and the hospital in services rendered to the community in their homes.

Lebanon Hospital for Mental and Nervous Diseases

The annual meeting of this hospital will be held at the Ambassadors' Hotel, Upper Woburn Place, London, W.C.1, on Thursday, June 19, at 4.45 P.M. Sir William Houston-Boswall will be in the chair, and the speakers will include Dr. E. Grey Turner, who has recently visited the hospital.

Royal Society of Medicine

On Wednesday, June 25, at 8.30 P.M., at a meeting of the section of orthopædics at 1, Wimpole Street, London, W.1, Lord Webb-Johnson, president of the society, will present the diploma of honorary fellowship to Dr. M. N. Smith-Petersen, of Boston.

School of Pharmacy, University of London

A Royal Charter of Incorporation has been granted to this school, which was founded in 1842 by the Pharmaceutical Society of Great Britain. It was financed by the society until 1949, when it was organised as an independent entity under its present title and financed through the University of London. The council of the school, which is composed of nominees of the university, the Pharmaceutical Society, the academic body of the school, and coöpted members, includes Sir Archibald Gray, Sir Henry Dale, O.M., Dr. Charles Harris, and Prof. G. A. H. Buttle. The chairman of the council is Sir Harry Jephcott, F.R.I.C.

Royal College of Midwives

At their annual meeting on June 5, the college reaffirmed its policy of opposition to the closed shop and passed a resolution deploring any suggestion that compulsory membership of an organisation should be required of midwives by employing authorities.

Miss Patricia Hornsby-Smith, parliamentary secretary to the Ministry of Health, speaking at a reception after the meeting, said that the continuing reduction in maternal and infant mortality was a tribute to the work and skill of the midwife. The provisional figures for last year were the lowest on record—infant mortality 29·6 per 1000 live births, and maternal mortality 0·81 per 1000 total births. But Sweden had a still lower infant mortality of 21 per 1000, and she wanted to see us achieve parity with our Scandinavian neighbour. She also welcomed the rise in the proportion of domiciliary midwives who administered gas-and-air analgesia from 52·8% in 1950 to 57·9% in 1951.

Conference on Nutritional Research

A European symposium on Present Problems in Nutritional Research is to be held under the auspices of the International Union of Nutritional Sciences at Basle, Switzerland, from Oct. 1 to 4. The local organiser is Prof. F. Verzár (Physiological Laboratory, University of Basle), to whom inquiries may be addressed. The hon. secretary of the union is Dr. L. J. Harris, Dunn Nutritional Laboratory, Milton Road, Cambridge.

Appointments

EARLE, B. VIGORS, M.D. Dubl., M.R.C.P.: senior grade full-time M.O., psychiatric department, St. Luke's-Woodside Hospital, London.

FISON, T. N., M.B. Camb.: appointed factory doctor, Sidmouth district, Devon.

LAING, STEPHANIE, M.R.C.S., D.P.H.: asst. county M.O. in the "excepted" district of Bromley, Kent.

LAWLESS, D. J., O.B.E., M.B., B.SC. N.U.I., D.P.H.: full-time consultant chest physician, West Ham chest clinic.

PRINCE, G. S., B.A., M.B. Dubl., M.R.C.P.I., D.P.M.: part-time consultant psychiatrist, Tilbury and Riverside (Orsett branch) General Hospital.

SIDDLE, S. G., M.D. Durh.: appointed factory doctor, Poulton-le-Fylde district, Lancaster.

SMYTH, D. A., M.B. Durh., D.P.H.: asst. county M.O., Worcestershire County Council.

WILSON, ROBERT, M.D. Dubl., F.R.C.P.I.: visiting physician, Royal City of Dublin Hospital.

Birmingham Regional Hospital Board:

MCKINNELL, J. S., M.B. Edin., DIP. PATH.: consultant pathologist, Birmingham (Selly Oak) group of hospitals.

MILLS, W. G., M.B. Birm., F.R.C.S., M.R.C.O.G.: consultant obstetrician and gynæcologist, Walsall group of hospitals.

POWELL-DAVID, J. D., M.D., B.SC. Wales: asst. chest physician, Wolverhampton group of hospitals.

RICHARDS, B. W., M.R.C.S., D.P.M.: con[illegible] deputy medical superintendent, St. [illegible]

SANDERSON, J. M., M.B. Birm., F.R.C.S [illegible] surgeon, Birmingham (Sanatoria) and Mid-Worcestershire group of hospitals.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Diary of the Week

JUNE 15 TO 21

Monday, 16th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
3.45 P.M. Mr. P. H. Mitchiner: Salivary Glands. (Arnot demonstration.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.1
4 P.M. Dr. Stephen Gold: Cutaneous Allergy.

ROYAL EYE HOSPITAL, St. George's Circus, S.E.1
5 P.M. Dr. T. H. Whittington: *Third-nerve Paralysis.*

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P.M. (Hammersmith Hospital, Ducane Road, W.12.) Dr A. M. Ramsay: Puerperal Infections.

UNIVERSITY OF EDINBURGH
5 P.M. (University New Buildings, Teviot Place.) Prof. Joh Hellström (Stockholm): Surgery of Urinary Calculi (First of three lectures.)

Tuesday, 17th

ROYAL COLLEGE OF PHYSICIANS, Pall Mall East, S.W.1
5 P.M. Dr. R. E. Lane: Blood Changes in Industrial Diseas (Ernestine Henry lecture.)

INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Street W.C.2
5.30 P.M. Dr. L. Musso: Modern Aspects of the Ground Sub stance, Collagen and Elastic Tissue.

SOUTH WEST LONDON MEDICAL SOCIETY
8.30 P.M. (Bolingbroke Hospital.) Dr. Courtenay Evans Paroxysmal Tachycardia.

UNIVERSITY OF EDINBURGH
5 P.M. Professor Hellström: Surgery of Urinary Calculi (Second of three lectures.)
5 P.M. Dr. Ernest Jawetz (California): Antibiotic Synergism and Antagonism. (Macarthur lecture.)

Wednesday, 18th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
11.45 A.M. Medical clinical-pathology conference.
3 P.M. Dr. Henry Aranow (New York): Phæochromocytoma.

ROYAL EYE HOSPITAL
5.30 P.M. Mr. R. P. Crick: Congenital Fundus Abnormalities

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: *Medical Mycology—Subcutaneou Mycotic Infections.*

UNIVERSITY OF EDINBURGH
5 P.M. Professor Hellström: Surgery of Urinary Calculi (Last of three lectures.)

Thursday, 19th

ROYAL COLLEGE OF SURGEONS
3.15 P.M. Prof. R. J. Last: The Larynx. (Arnott demonstration.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. Paul Wood: Pulmonary Hypertension.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4 P.M. (Queen Charlotte's Maternity Hospital, Goldhawk Road, Hammersmith, W.6.) Prof. H. Alvarez, Prof. R. Caldeyro-Barcia (Montevideo): Uterine Contractility.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W.1
5 P.M. Dr. Partridge: Psy[illegible]try

WEST LONDON HOSPITAL MEDICAL [illegible] W.6
8.30 P.M. Mr. Murray A. Falcone[illegible] Treatment of Intracrani[illegible] [illegible] -Smith lecture.)

Friday, 20th

UNIVERSITY OF LONDON
5 P.M. (University College Hospital Medical School, University Street, W.C.1.) Professor Alvarez, Professor Caldeyro-Barcia: Physiology of Uterine Action.

POSTGRADUATE [illegible] LONDON
11.15 A.M. [illegible] conference.
2 P.M. Dr. [illegible] Colitis.
4 P.M. Mr. W. P. Cleland: Surgical Aspects of Acquired Heart-disease.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. D. I. Williams: Erythrodermias.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4.30 P.M. (Chelsea Hospital for Women, Dovehouse Street, S.W.3.) Mr. W. Hawksworth: Carcinoma of the Corpus Uteri.

FACULTY [illegible]
9.30 A[illegible] Infirmary, Newcastle upon Tyne.)
11 A.M. [illegible] Dr. G. A. Neligan, Dr. C. K. Warrick: Osteitis in Childhood. Dr. G. Davison, Dr. T. R. Harlan: Intestinal Obstruction in the Neonatal Period.
2.30 P.M. *Therapy section.* Mr. W. R. Douglas, Mr. C. J. L. Thurgar, Dr. J. R. Nuttall: Treatment of Squamous-cell Carcinoma in Lymphatic Glands.

Saturday, 21st

BIOCHEMICAL SOCIETY
11 A.M. (School of Biochemistry, Tennis Court Road, Cambridge.) Scientific papers.

FACULTY OF RADIOLOGISTS
10 A.M. *Diagnosis and Therapy sections.* Dr. H. R. Sear (Sydney), Sir James Spence, Mr. I. G. Williams: Letterer-Siwe's Disease and Allied Conditions.

EXPOSURE OF FACIAL NERVE

Facial palsy in itself is harmless, and so there have been few opportunities for detailed histological examination of the nerve-trunk and its coverings. Much of what is at present known about the nature and situation of the various lesions responsible for the paralysis is the result of direct inspection by naked eye and by dissecting-microscope giving ten diameters of magnification (Cawthorne 1941). Such observations have been limited to those cases in which the severity and duration of the palsy have warranted operation, and of course by the extent to which the nerve can be exposed without interfering with function of neighbouring structures.

It will be appreciated that many cases of peripheral facial paralysis recover without any surgical intervention or, for that matter, without any form of special treatment. It is for this reason that, in the past, it has been the general custom in all cases of facial paralysis—no matter what the cause—to adopt an expectant attitude, even though, as we now know, the nature of the lesion causing the paralysis made spontaneous recovery impossible. When, in the course of time, it became evident that the paralysis was permanent, it was sometimes found useful to unite the facial nerve-trunk in the face with a neighbouring motor nerve—the spinal accessory or the hypoglossal. This procedure was introduced by Ballance in 1894.

Alt (1908) was the first to describe direct exposure of the facial nerve-trunk in cases of paralysis. Ney (1922) made a contribution to the appreciation of the problem which foreshadowed much of the work which was to follow. Mackenzie (1922), Bunnell (1927), Smith (1931), and Martin 1931) were all in favour of exposure of the nerve-trunk n suitable cases. Ballance was not satisfied with his anastomosis operation and, at an age when most workers would be content in retirement, he again attacked the problem; and the combined work of Ballance and Duel (1932) led to general acceptance of the principle that, in severe peripheral facial palsy, consideration should be given to exposure of the nerve-trunk at the site of the lesion. Since then their findings have been confirmed and additional features recorded by many workers, including Tickle (1945), Morris (1936), Sullivan (1938), Sullivan and Smith (1950), Cawthorne (1938, 1946, 1951), Fowler (1939), Collier (1940, 1949), Kettel (1943, 1947, 1950), and Findlay (1950).

It is important to know when the nerve should be exposed and when it should be left alone. To await spontaneous recovery, which, because of the nature of the lesion, cannot take place may be to rob the patient of the chance of a good recovery; while to operate when spontaneous recovery is likely may hinder the good work of Nature and encourage bad surgical judgment.

In general it can be said that exploration of the nerve should be considered in case[illegible]plete paralysis in which there is no sign (elect[illegible]nical) of returning function after a month, an[illegible]e lesion is thought to be surgically accessible. [illegible]l nerve-trunk from the parotid gland up alm[illegible] the geniculate ganglion can be exposed without u[illegible]uly interfering with neighbouring structures and their function. Exposure beyond the ganglion, though not impossible, is not easy and is likely to jeopardise cochlear and vestibular function. In cases where the paralysis immediately follows an injury likely to affect the nerve—this applies particularly to suspected surgical damage—the nerve should be explored without delay, so that any bony fragments pressing on the nerve can be removed, and any additional damage to nerve-fibres from pressure due to reactionary swelling can be prevented by decompression. When there is a clear interval between the injury and the onset of the paralysis, it is reasonable to wait, for spontaneous recovery is usual. When facial palsy accompanies an acute aural infection, spontaneous recovery is the rule, but in the case of a chronic infection operation is always indicated. Facial palsy with herpes should not be submitted to operation. Exposure in Bell's palsy should only be considered when the paralysis is complete, because full spontaneous recovery is the rule when the palsy is incomplete. Of 106 cases of Bell's palsy in which the paralysis was complete 57 still showed no sign of recovery after two months (Cawthorne 1951); and even though after this time some did get a degree of spontaneous recovery, it was far from complete. It is customary to wait for a month at least for signs of spontaneous recovery, but in complete paralysis, particularly if there is much pain at the onset, earlier operation may be considered. Certainly the best chance of a complete recovery in a severe case is to be expected from very early decompression, but at present there is no definite proof of a complete nerve block in the early stages. As soon as such proof is available, decompression should be done with the least possible delay. Tumours—e.g., primary cholesteatoma and neurofibroma—will, of course, need operation as soon as the true nature of the condition is suspected.

In estimating the severity of the lesion it is customary to rely on the degree of paralysis, on the electrical reactions of the nerve and muscles found by applying *the interrupted faradic and galvanic current to the* nerve and muscles, and on the electromyogram. The electrical reactions should be studied in every case, because they indicate the state of the muscles and of the nerve-trunk, and this information should always be available before starting an operation.

When exposure of the nerve is contemplated, it is necessary to have some idea of the probable situation of the lesion in the nerve-trunk. When the lesion is extracranial, there is usually a wound or a swelling to guide the surgeon to the site. With intratemporal lesions the site, when surgically accessible, is between the stylomastoid foramen and the geniculate ganglion. Taste will probably be lost on the anterior part of the tongue on the affected side, for the chorda tympani nerve carrying taste fibres joins the facial trunk only a few millimetres above the stylomastoid foramen. If, however, lacrimation on the same side is deficient or absent, this means that the lesion is at, or proximal to, the geniculate ganglion and so is not easily reached. Between these two levels the only guide to the site of the lesion is the cause. Some indication of this may be gained from table II, which shows the relationship of the site to the cause in 129 cases of facial palsy where the nerve was explored and the lesion found to be intratemporal. Three sites have been chosen—tympanic, bend and upper vertical, and lower vertical—because the approach is slightly different in each. Exposure of the tympanic segment usually means interfering with hearing, because the incus may have to be removed. The approach to this segment is easier by the endaural route. The conventional approach to the mastoid antrum is used for the bend and upper vertical segment; the lower vertical segment should be approached by the postaural route, and it may not be necessary to encroach on the mastoid antrum at all.

TABLE II—CAUSE AND SITE OF LESION IN 129 CASES OF INTRATEMPORAL FACIAL PALSY SUBMITTED TO OPERATION

A. TYMPANIC SEGMENT	..	28
Injury	17	
Infection	9	
New growth	2	
B. BEND AND UPPER VERTICAL SEGMENT ..	..	46
Injury	28	
Infection	15	
New growth	3	
C. LOWER VERTICAL SEGMENT	..	55
Bell's palsy	53	
Injury	2	

The operation for exposure of the facial nerve is safe, convalescence should be uneventful and quick, and in many cases the wound of entry can be closed so that healing is by first intention.

THE RÔLE OF SURGERY IN THE INVESTIGATION AND TREATMENT OF PERIPHERAL FACIAL PALSY*

TERENCE CAWTHORNE
F.R.C.S.
AURAL SURGEON, NATIONAL HOSPITAL FOR NERVOUS DISEASES, LONDON

THE facial nerve is more often paralysed than any other *motor* nerve, perhaps because it has a longer course in a bony canal than has any other nerve in the body.

In its long tortuous journey through the temporal bone to the face the facial nerve winds outwards and then backwards round the labyrinth, and next turns downwards between the middle ear and the mastoid to emerge at the stylomastoid foramen after a journey of about 35 mm. in the narrow bony fallopian or facial canal. From the stylomastoid foramen it winds forwards round the lower margin of the pinna for another 30 mm. before dividing into its terminal branches in the parotid gland in front of the ear. Thus it is in close contact with the external, middle, and internal parts of the ear, and may be involved in any disease or injury affecting them.

SITES OF LESIONS

The facial nerve first enters the temporal bone by the wide shallow funnel of the internal auditory meatus in close company with the auditory nerve. Though here it may be pressed upon by an acoustic neurofibroma, there is plenty of room for expansion; hence any result other than a slight weakness of the face is unusual. Edwards and Paterson (1951), in a review of the signs and symptoms of acoustic neurofibromata in 157 cases, though they noted slight facial weakness in 99, found almost complete paralysis in only 6. Discussing the effect of acoustic tumours on the facial nerve Cushing (1917) remarked: "The nerve may be elongated in its course to an amazing degree without producing any palsy whatever." This hardiness is, however, lost as soon as the facial nerve enters the fallopian canal at the fundus of the internal auditory meatus. From here, until it emerges at the stylomastoid foramen, the nerve is vulnerable, and complete paralysis can be induced by comparatively trifling lesions.

This is shown by the fact that the lesion causing peripheral facial paralysis is usually in the nerve as it lies in the bony canal distal to the geniculate ganglion. Gowers (1893) was fully aware of this: "A complete unilateral palsy of the face, without other symptoms must mean disease of the nerve as it passes through the bone."

Table I gives the causes and the probable sites of the lesions in the facial nerve in 325 cases of peripheral facial paralysis seen in the past fifteen years for which records are available. The sites of the lesions were verified at operation in 144 cases and are classified as: (1) *intracranial*, in which the lesion is in the nucleus or in the nerve-trunk before it enters the fallopian canal; (2) intratemporal, within the canal; and (3) extracranial, after the nerve has left the stylomastoid foramen. Cases of multiple cranial-nerve palsies and those in which the palsy has accompanied acute otitis media are excluded.

Though the vulnerability of the facial nerve during its passage through the temporal bone can be partly explained by the presence of its troublesome neighbour the ear, the principal reason is that the facial nerve lies firmly encased in a bony canal. Any damage to the bony facial canal from extension of a basal skull fracture or from the aural surgeon's gouge or curette will bruise, crush, or cut the nerve, which being imprisoned in the bony canal cannot avoid injury by being pushed aside, as would probably happen if it were free to move. Further, there is no room for expansion; hence any reactionary swelling or bleeding within the canal as the result of injury will cause further damage by pressure. Infection spreading to the facial canal from the adjacent spaces in the middle and internal ear may cause the nerve to swell in its narrow canal and thus produce compression. Finally, there is the swelling of the nerve in the canal just above the stylomastoid foramen in cases of Bell's palsy. Such cases form such a large proportion of the whole group that further inquiry into the nature and causes of Bell's palsy is necessary.

TABLE I—CAUSES OF PERIPHERAL FACIAL PARALYSIS IN A SERIES OF 325 CASES.

INTRACRANIAL		9
New growth	4	
Disseminated sclerosis	2	
Poliomyelitis	3	
INTRATEMPORAL		301
Bell's palsy	205	
Injury	47	
Otitis media	26	
Herpes	18	
New growth	5	
EXTRACRANIAL		15
Injury	12	
New growth	3	

BELL'S PALSY

Once again that careful observer Gowers (1893) noted in respect of Bell's palsy:

> "The features of these cases are so uniform, allowance being made for differences in degree, that we are justified in regarding the pathological condition as the same in all—a neuritis within the fallopian canal. It has been conjectured that the inflammation sometimes affects the nerve after its emergence, but no evidence of this has been noted. The inflammation perhaps affects chiefly the sheath of the nerve, which swells and compresses the fibres, expansion outwards being prevented; but in a case in which the actual state could be observed (Minkowski, *Berlin. Klin. Wochenschr.* 1891) the nerve sheath was not distinctly inflamed; the external restraint may indeed cause the inflammation to spread into the nerve, and in this case fibres were extensively degenerated."

Ballance and Duel (1932) and other observers who have examined the nerve-trunk in the living in severe and long-continued Bell's palsy have also noted that the nerve-trunk just above the stylomastoid foramen appeared swollen, even to the naked eye. A more detailed examination in such circumstances has been made possible by using a binocular dissecting-microscope giving 10 diameters of magnification. The following appearances have been noted (Cawthorne 1946):

> The sheath of the nerve consists of several layers, the outer layer being thick and the inner layers very thin indeed. The nerve-trunk when eventually exposed seems to be unduly constricted at the stylomastoid foramen. There is a natural though slight narrowing here, but in Bell's palsy this is accentuated by swelling of the nerve above this level. At and just above the constriction there are usually one or more thin hæmorrhagic streaks, about 2 mm. long, in the axis of the nerve. Above the constriction the nerve-trunk swells out, the swollen segment extending upwards for 5–10 mm. before tapering off. In this swollen segment the nerve may be discoloured by pink patches here and there, and in a few cases it has been deep reddish purple.

Thus, though there can be no doubt about the site and gross appearance of the lesion in most of the cases grouped under the heading of Bell's palsy, the cause still remains unexplained. The term neuritis suggests an inflammation, but the appearances seen are more likely to be the result of ischæmia than of infection.

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* Based on a lecture given at the Royal College of Surgeons on April 21, 1952.

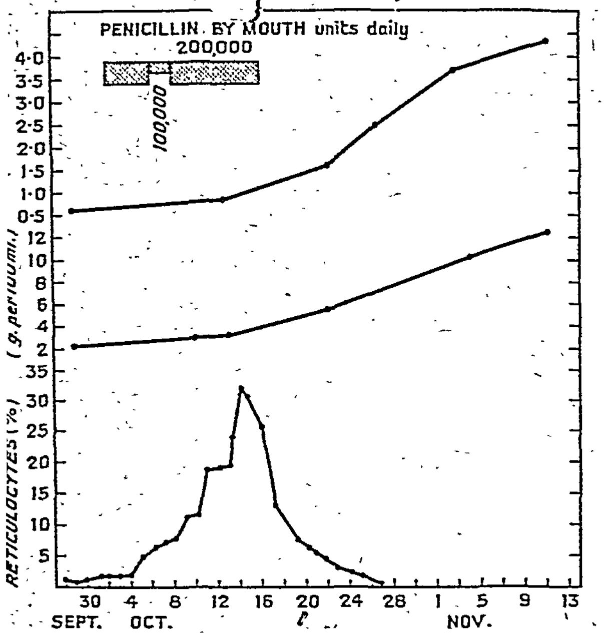


Fig. 1—Treatment and hæmatological findings of case 1.

CASE-RECORDS

Case 1.—A man, aged 30, of the Boran tribe from Somali-
ıd, entered the King George VI Hospital, Nairobi, on
pt. 28, 1951. He was well nourished and of good physique;
ither his spleen nor his liver was palpable. He was icteric
d obviously ill. There was no œdema either of his back or
ankles, and his tongue, teeth, nails, and reflexes were all
rmal. His heart and lungs showed nothing incompatible
th his severe anæmia. He was afebrile and continued to be
throughout his stay in hospital.

Blood examination on Sept. 29 showed: red cells, 607,000
r c.mm.; Hb, 2·1 g. per 100 ml.; hæmatocrit, 7·5%;
ticulocytes, 1%; mean corpuscular volume, 123 c.µ; mean
rpuscular Hb, 35 µµg.; mean corpuscular Hb concentration,
%; Schumm's test, ++++; indirect van den Bergh
st, bilirubin 2·5 mg. per 100 ml.; white cells, 2300 per
mm.; no sickling; Kahn test, negative on three occasions;
ıd no malaria parasites.

Sternal puncture on Oct. 2, showed a low-activity marrow
ith many megaloblasts, giant stab-cells, and erythropoiesis
ı the megaloblastic side.

Treatment and Progress.—The patient was kept under
bservation without treatment from Sept. 28 until Oct. 2,
uring which time the reticulocytes varied between 1·5% and
·0%. Treatment was with oral crystalline penicillin G (Glaxo)
00,000 units twice daily from Oct. 2 to Oct. 6, 50,000 units
wice daily from Oct. 6 to Oct. 8, and 100,000 units twice
aily from Oct. 8 to Oct. 16. After the twelfth day of this
reatment the proportion of reticulocytes increased to 32%.
ternal puncture on Oct. 12 showed a moderately active
arrow mainly erythroblastic, with very scanty megaloblasts
ıd giant stab-cells. He was discharged from hospital fit and
ell on Nov. 12 with red cells 4,100,000 per c.mm. and Hb
2 g. per 100 ml. No treatment other than oral penicillin had
een given. A gastric test after histamine on Oct 21, showed
ypochlorhydria, the maximum free acid being equivalent
o 18 ml. of N/10 sodium hydroxide, with normal pepsin.
he patient's hæmatological progress is shown in fig. 1.

Case 2.—A female Jaluo in the eighth month of pregnancy
ntered the hospital on May 21, 1951, because of weakness,
lyspnœa, and general debility; she was afebrile and remained
so.

On examination she was a well-nourished and well-developed
voman aged about 25. Neither the spleen nor the liver was
palpable. There was nothing abnormal in her chest, and her
neart showed nothing that could not be accounted for by her
næmia. She was icteric, there was no œdema of the legs or
and the tongue, teeth, and nails were normal. The
ous system showed nothing abnormal.

lood examination on May 25 showed: red cells, 1,082,000
c.mm.; Hb, 3·3 g. per 100 ml.; hæmatocrit, 12·5%;
locytes, 1·5%; mean corpuscular volume, 115 c.µ;
cells
Hb

mean corpuscular Hb,
centration, 26·4%; Schu
Bergh test, bilirubin 3 mg. p
c.mm.; no sickling; Kahn test, neg tive; an
parasites.

Stools contained ova of ascaris and tænia.

Sternal puncture on May 25 showed a marrow næmia. She had
containing many intermediate megaloblasts a which had been
cells. en we saw her

Treatment and Progress.—The patient wa well-developed
observation from May 21 until May 26, with n, the youngest
whatever, and during this period her retic laria as a child.
between 1·0% and 1·5%. Treatment was with nd liver neither
penicillin G 100,000 units twice daily from Ma ue were normal.
50,000 units twice daily from June 2 to June ; toe; otherwise
units twice daily from June 7 to June 12. Af no œdema or
penicillin the reticulocytes were 30% and not contain any
1,652,000 per c.mm. Sternal puncture on June
active marrow with an erythroblastic picture, 1950, showe
of the megaloblastic series and very rare giant st 100 ml.; mea
June 12 the patient went into labour and left n Bergh te
On June 13, she was delivered of a male bab est; +++ t,
on June 16. On June 20 the patient's red cells w intermedi
per c.mm., and Hb was 7·4 g. per 100 ml., and ric test a ed
and about. A gastric test after histamine on June dic
a hypochlorhydria equivalent to 10 ml. of N/1 bserv ort
hydroxide. Pepsin was normal. e-aine)

Follow-up.—This woman visited us as an outpatient ther
July 27, when her red cells were 4,470,000 per c.mm., and night
Hb was 12 g. per 100 ml. The blood findings are show
fig. 2. 9 g.

As it is well known that, after delivery, especi
the baby is not being breast-fed, there is often sponta Fe and
remission of anæmia, the blood findings in this lowed
after June 12 cannot be regarded as entirely signific ase of
but the maximum reticulocyte response, with) first
doubling of the red cells and hæmoglobin, and rever ocking
of the marrow to normal, all took place within two we n this
and before the baby was born. aterial
tes it

Case 3.—A male Jaluo, aged about 20, entered the hospi olog
on June 26, 1951, with red cells 2,780,000 per c.mm. and
Hb 6 g. per 100 ml. He was not, however, seen by us until July 6, when examination showed a well-nourished and well-developed male with no visible icterus and no œdema. His spleen was II (Hackett) and his liver slightly tender. His tongue, nails, and teeth were all normal, and his nervous system showed nothing abnormal. His chest and heart were also normal. He was afebrile.

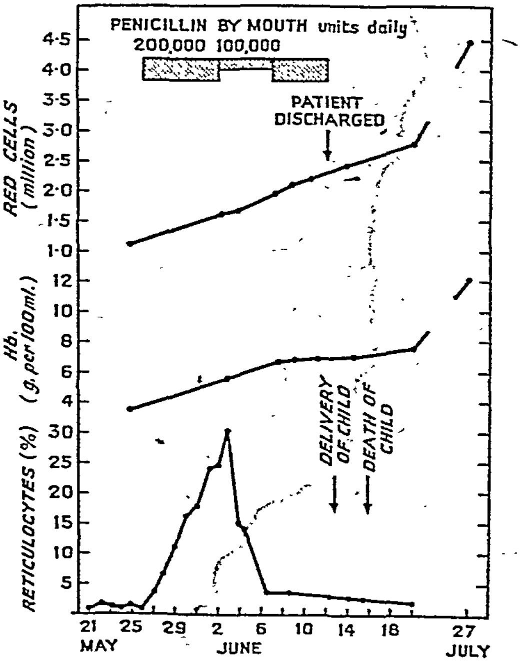


Fig. 2—Treatment and hæmatological findings of case 2.

ılls for special experi-
on after the surgeon has
THE practic e cadaver.
ulation the nerve and its sheath is best
INVESTI gnified field, and for this the dissecting-
PER advised. Such a microscope not only
ecognition of pathological changes but also
e handling of the nerve. Moreover, in cases
re there may be some difficulty in picking
AURAL SUR from the mass of fibrous and granulation
ıding the injured area, the microscope
task and may even enable a few precious
THE facial ve to be preserved intact. It is more impor-
other motor microscope for the finer part of facial-nerve
course in a b for any other surgery of the temporal bone.
body. on has been located, the nerve-sheath above
In its lon he lesion should be exposed until normal
bone to the een found. Then it is usually necessary to
then backw eath and inspect the nerve-trunk. For this,
downwards lmic instruments are needed. In cases of
emerge at t urviving strands of nerve should be carefully
about 35 m because even a small intact strand of nerve may
canal. F e the pressure has been relieved, and the func-
round t result will be much better than from a graft. Any
befor in the nerve should be bridged with a fresh nerve
gland after all fibrous or granulation tissue has been
with lly trimmed away from the site of the injury. If
ear, a le, the ends of the nerve should be brought together
affecti ıt a graft, but it is wiser not to attempt this by
ing the nerve from its bony canal, which acts as
The ful splint during the period of regrowth.
the w many cases—this applies particularly to Bell's
in cl —simple decompression is all that is needed.
here fore the wound is closed, the exposed nerve should
fibro covered with a single layer of prepared amniotic
any nbrane.

unum the face the mechanical problems are a little different, and relief of pressure from bone fragments or swelling is not called for. Wide gaps can be effectively bridged with nerve grafts, as shown by Lathrop (1946) in extensive war wounds.

Where the continuity of the nerve has not been entirely lost there is often an early return of facial movement, due to the relief of pressure on nerve-fibres which, though dead to electrical tests, recover quickly after decompression. In traumatic cases with a complete section it will be several months before there is any movement. During the period of waiting the facial muscles must be kept in good trim by massage and gentle galvanic stimulation. A hook fixed to a dental plate is a convenient support for a drooping mouth. Once facial movements have started, galvanism should be stopped and active exercises in front of a mirror encouraged. The mouth needs special attention; this was realised in the 16th century by Velascus, who ordered his patients with facial palsy to carry a trumpet and sound it frequently. Nowadays the tin whistle and mouth-organ serve the same purpose.

Where the nerve has been damaged or diseased in a site not easily accessible to surgery—e.g., at the internal auditory meatus in the case of acoustic neurofibromata—return of facial movements may follow anastomosis in the neck of the peripheral end of the facial nerve-trunk with a neighbouring motor nerve, either the spinal accessory or the hypoglossal. Should this fail, and in long-standing cases where the facial musculature has atrophied, plastic procedures are indicated.

Thus exposure of the facial nerve-trunk at the site of the lesion in severe facial paralysis serves the double purpose of increasing appreciation of the causes and mechanism of this condition and of being the first step in the treatment of the lesion. By relieving pressure it encourages return of natural function where the nerve-trunk is intact. Where continuity of the nerve-trunk is lost, restoration by means of end-to-end apposition or the insertion of an autogenous nerve graft will usually enab facial movements to be restored.

REFERENCES

Alt, F. (1908) *Verh. dtsch. Otol. Ges.* **191**, 1908.
Ballance, C., Duel, A. B. (1932) *Arch. Otolaryng., Chicago*, **15**, 1.
Bunnell, S. (1927) *Surg. Gynec. Obstet.* **45**, 7.
Cawthorne, T. (1938) *Trans. Med. Soc. Lond.* **60**, 171.
— (1941) *Proc. R. Soc. Med.* **34**, 582.
— (1946) *Laryngoscope*, **56**, 653.
— (1951) *Proc. R. Soc. Med.* **44**, 565.
Collier, D. J. (1940) *Lancet*, ii, 91.
— (1949) *J. Amer. med. Wom. Ass.* **4/10**, 401.
Cushing, H. W. (1917) Tumours of the Nervus Acusticus. Pl adelphia and London; p. 165.
Edwards, C. H., Paterson, J. H. (1951) *Brain*, **74**, 144.
Findlay, J. P. (1950) Facial Paralysis. Sydney.
Fowler, E. P. jun. (1939) *Acta oto-laryngol., Stockh.* **27**, 615.
Gowers, W. R. (1893) A Manual of Diseases of the Nervous Syste 2nd ed., London; p. 229.
Kettel, K. (1943) *Arch. Otolaryng., Chicago*, **37**, 303.
— (1947) *Ibid*, **46**, 427.
— (1950) *Ibid*, **51**, 25.
Lathrop, F. D. (1946) *Laryngoscope*, **56**, 665.
Mackenzie, D. (1922) La paralysie faciale et son traitement. Pa
Martin, R. C. (1931) *Arch. Otolaryng., Chicago*, **13**, 259.
Morris, W. M. (1936) *Lancet*, ii, 1172.
Ney, K. W. (1922) *Laryngoscope*, **32**, 327.
Smith, J. M. (1931) *Ann. Otol., &c., St. Louis*, **40**, 1179.
Sullivan, J. A. (1938) *Canad. med. Ass. J.* **39**, 451.
— Smith, J. B. (1950) *Ann. Otol. Rhino. & Laryng.* **59**, 1148.
Tickle, T. G. (1945) *Laryngoscope*, **55**, 191.

RESPONSE OF MEGALOBLASTIC ANÆMI IN AFRICANS TO ORAL CRYSTALLINE PENICILLIN G

HENRY FOY
M.A., Ph.D., D.Sc. Oxfd

ATHENA KONDI
M.D. Athens

Of the Wellcome Trust Research Laboratories

A. HARGREAVES
M.A., M.B. Camb.

J. LOWRY
M.B. Belf.

Of the Colonial Medical Service, Kenya

WE have already reported that the megaloblast anæmias of Africans (both pregnant and non-pregnan respond to intramuscular crystalline penicillin G in t same way as they respond to liver, folic acid, or vitam B_{12} (Foy et al. 1951). There is a maximum speci reticulocyte response followed by the expected regener tion of red cells and hæmoglobin, which double them selves within two weeks from the beginning of treatmen

We attributed these effects to a selective action penicillin on the intestinal flora. The antibiotic ma prevent growth of micro-organisms which compete f the essential hæmopoietic factors, and thus leave a cle field for those which synthesise these factors.

Numerous investigators working with various ant biotics in various groups of animals have found that the stimulate growth and/or reduce mortality in the youn This growth-promoting and/or ı is sometimes seen in the presc sometimes in its absence, and it can be explained eithe by the antibiotic "sparing" vitamin B_{12} or by i changing the microflora of the gut as suggested above.

We report here the responses of megaloblastic anæmia in Africans to oral crystalline penicillin G, and emphasis that the *dosage*—whether of oral or parenteral penicillin—is of great importance.

Below are given the results of treating representativ cases of megaloblastic anæmia with oral penicillin. Tw were treated with small doses (200,000 units daily) an two with large doses (400,000–600,000 units daily) Those treated with small doses responded, but *thos treated* with large doses did not. The probable explana tion of this is that the large dose destroys not only thos bacteria which are competing for the essential hæmo poietic substances but also the bacteria synthesis *these factors.* Had the effect been due to the antibio content of unknown hæmopoietic substances, the la doses should have produced results as good as, or be than, the small doses.

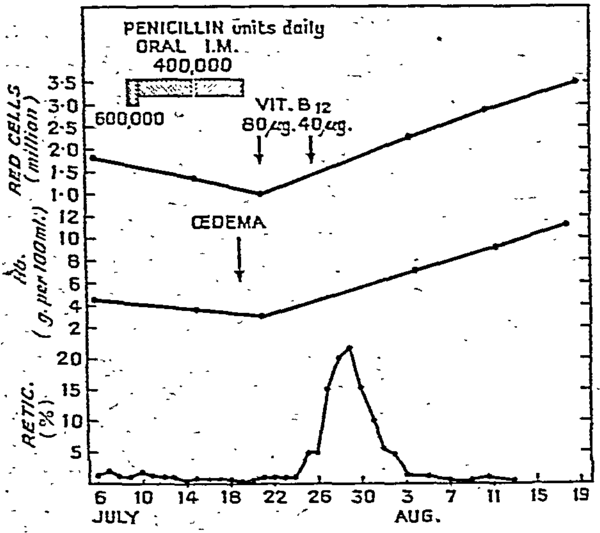


Fig. 3—Treatment and hæmatological findings of case 3.

Previous History.—This man had been under our care because of severe anæmia in December, 1949, and had been then successfully treated with parenteral crystalline penicillin G 400,000 units daily.

Blood examination on July 6 showed: red cells, 1,800,000 per c.mm.; Hb, 4·6 g. per 100 ml.; hæmatocrit, 16%; reticulocytes, 1%; mean corpuscular volume, 89 c.μ; mean corpuscular Hb, 26 μμg.; mean corpuscular Hb concentration, 29%; Schumm's test, +++; indirect van den Bergh test, bilirubin 1 mg. per 100 ml.; white cells, 2275 per c.mm.; no sickling; Kahn test negative; and no malaria parasites.

Stools contained no ova or parasites.

Sternal puncture on July 6 showed an active marrow with many typical orthochromatic megaloblasts of Ehrlich and giant stab-cells.

Treatment and Progress.—The patient was kept under observation without treatment from July 6 to 9, during which time his reticulocytes (fig. 3) varied between 1% and 2%. He was given oral crystalline penicillin G 600,000 units on July 9 and 400,000 units daily from July 10 to July 15. During this period his condition deteriorated rapidly. He was vomiting, had diarrhœa, and complained of headaches and pains all over the body. The reticulocytes during this period of oral penicillin never increased above 1%. Sternal puncture on July 16 showed no change in the marrow, the orthochromatic megaloblasts and giant stab-cells still being present.

The deterioration was at first attributed to the presence of free hydrochloric acid in the gastric juice (equivalent to 105 ml. of N/10 sodium hydroxide) which was thought to be destroying the penicillin, and the patient was therefore given intramuscular crystalline penicillin G 400,000 units daily from July 15 to 20. This was done in view of his previous response to parenteral penicillin 400,000 units daily given in the previous year. As will be seen from fig. 3, there was no response, and the patient continued to deteriorate, œdema of the face and legs appearing on July 19. His red cells on the 21st were only 1,000,000 and Hb 3·6 g. per 100 ml. He was given vitamin B_{12} 80 μg. by injection on July 21, and 40 μg. on the 26th. Fig. 3 shows that the reticulocytes increased to 5% on July 25 and to 22% on the 29th. On Aug. 4 the red cells were 2,400,000, and Hb 7·4 g.

The patient left the hospital at his own request on Aug. 18 when his red cells [illegible] 3,416,000 per c.mm.

Henry on Nov. 1, 1950, as having pernicious anæmia. She had had several previous relapses of anæmia, which had been successfully treated with liver injections. When we saw her she was a non-pregnant, well-nourished, and well-developed woman aged about 32. She had three children, the youngest being aged 5 years. She gave a history of malaria as a child.

Examination showed spleen P (Hackett), and liver neither palpable nor tender. Nails, teeth, and tongue were normal. There was slight insensitivity of the left great toe; otherwise she had no nervous affection. There was no œdema or malaria, and she was afebrile. Her stools did not contain any ova or cysts. She was icteric.

Blood examination on admission on Nov. 1, 1950, showed red cells, 1,610,000 per c.mm.; Hb, 4·1 g. per 100 ml.; mea corpuscular volume, 86 c.μ; indirect van den Bergh te bilirubin 2·6 mg. per 100 ml.; and Schumm's test, +++. Sternal puncture showed a marrow with many intermedi megaloblasts and giant stab-cells. A gastric test a histamine showed complete achlorhydria.

Treatment and Progress.—She was kept under observ for ten days, during which time her reticulocyte remained stable. She was given vitamin B_{12} 80 μg. by inj and responded with a reticulocytosis of 26%. No other ment whatever was given, and she left the hospital on N 1950, with red cells 3,565,000 per c.mm. and Hb 9 g. 100 ml.

Follow-up.—She visited us as an outpatient on F 1951, when her red cells were 4,220,000 and Hb 11 g. the interval she had no treatment.

Readmission (fig. 4).—Four months later, on May 31, readmitted with severe anæmia. Examination showe the same state of affairs as before.

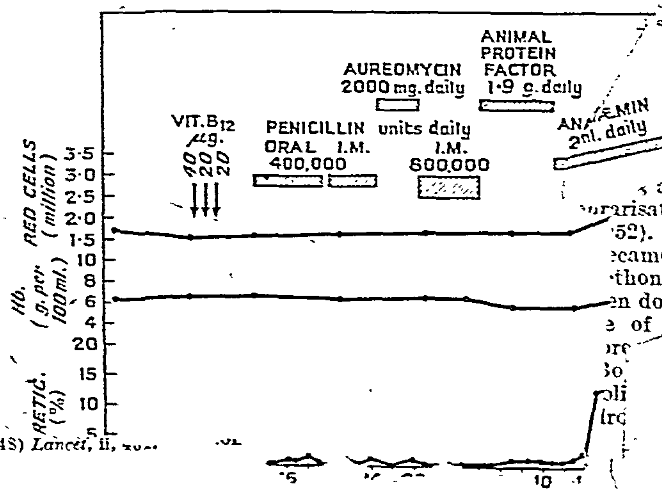
Blood examination on May 31 showed: red cells, 1 per c.mm.; Hb, 6·3 g. per 100 ml.; reticulocyt hæmatocrit, 17·5%; mean corpuscular volume, mean corpuscular Hb, 38 μμg.; mean corpuscular centration, 36%; colour-index, 1·3; Schumm +++++; indirect van den Bergh test, bilirub per 100 ml.; no sickling; Kahn [illegible] negative; 2800 per c.mm.; and no malaria parasites orthochromatic megaloblasts of Ehrlich in the

Stools showed no ova or cysts.

Sternal puncture showed a pernicious-anæmia p many typical megaloblasts and giant stab-cells.

Treatment and Progress.—The patient was k observation without treatment from May 31 to Ju during which time the proportion of reticulocyt increase. On June 7 the red cells were 1,550,000 On that date she was given vitamin B_{12} 40 μg. ascertain whether intrinsic factor was present in juice, and on each of the next two days she rec As will be seen from fig. 4, this gave rise to no r her condition began to deteriorate. She was vor unwell, and had no appetite.

Treatment with oral crystalline penicillin G daily was begun on June 13 and continued There was no improvement in the patient's co



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1218 LANCET] …lls for special experi- insertion of an autogenous nerve graft will usually enable

… not rise. Treatment with intramuscular …e 400,000 units was begun on June 20 …he 24th. On June 21 her red cells were 1,570,000 and Hb 6·3 g. per 100 ml. From the 25th to the 28th she was given 8 capsules of aureomycin daily (aureomycin hydrochloride 250 mg. per capsule) without response. On the 29th treatment reverted to parenteral crystalline penicillin G 800,000 units daily for five days. As will be seen from fig. 4, there was no response.

On July 4, she was given 9 capsules of animal protein factor ('Aurofax,' Lederle) daily for seven days. There was no response. On July 9, sternal puncture showed a marrow of moderate activity with megaloblasts and giant stab-cells. …eatment with 'Anahæmin' 2 ml. daily was begun on July 11, …d continued until the 22nd. After seven injections of …ahæmin the reticulocytes increased to 20%. The patient … the hospital on Aug. 1, with red cells 3,110,000 per c.mm. … Hb 9 g. per 100 ml. She visited us on Sept. 1, when her …cells were 4,370,000 and Hb was 10 g. per 100 ml. During …period she had been given 2 ml. of anahæmin weekly. The … findings are shown in fig. 4.

DISCUSSION

… in the previous cases treated with intramuscular …cillin, typical responses have now been obtained with … penicillin in the megaloblastic anæmias of Africans. …e was, however, a considerable difference between …sponses to small and large doses.

…s 1 and 2, in which not more than 200,000 units …ven daily, showed typical responses. There was …ase in the reticulocytes, followed by a doubling of …oglobin and red cells within fourteen days of the … treatment. The marrow also returned to normal. … 3 and 4, in which 400,000–600,000 units was …aily, showed no response. The reticulocytes did …ge and the red cells and hæmoglobin decreased. … 3 the …ility that the normal gastric … respons… for the failure of oral penicillin …dered; but, since the patient also did not … intramuscular penicillin given later, gastric …not be regarded as the cause of the failure. …n, case 4, in which there was a complete …fast achlorhydria, also did not respond to …illin. It is also now known that penicillin is …not destroyed by gastric acid.

…ast, deficiency of first-class protein has been …s the primary and exciting cause in the …he nutritional megaloblastic anæmias, in spite …hat very few such cases responded to a protein …d respond to such hæmopoietic substances …min B_{12}, folic acid, and 'Marmite.' …inion that a combination of a low-protein …ulky carbohydrate intake acts indirectly …h microflora that is inimical to the synthesis …ation of hæmopoietic factors by the host.

…onsider that the high frequency of diseases …ency of members of the vitamin-B complex …, India, the Balkans, and elsewhere may … fact that the bacterial intestinal environ- … such a dietary imbalance prevents the …nd/or utilisation of the vitamin-B …on is borne out by the response … like pellagra give to penicillin …published).

…rthy that almost none of the cases of …emia that we have seen in Macedonia, …ny parts of Africa show any signs of … Most of our patients were well nourished …h a layer of subcutaneous fat.

… in cases 3 and 4 was, we believe, … the synthesising as well as the …lora of the gut by the large doses of

…ar that the responses of megalobl…tic …in are not d… to no… con…

As pointed out in previous papers, there is no question of the hospital diet having entered into the picture. We have often had patients in hospital for two or three weeks and they have shown no reticulocytosis and no improvement in the blood. This is illustrated in case 4.

Ungley (1951) has suggested that the important feature in pernicious anæmia is gastric atrophy, which may lead not only to loss of vitamin B_{12} but also to changes in the bacterial flora of the upper intestine, and the formation of toxic substances.

In pernicious anæmia, no doubt, it is the gastric secretion, rather than the diet, that is at fault: the achlorhydria causes changes in the microflora which in turn cause anæmia. As knowledge accumulates, it is becoming more and more difficult to distinguish between true pernicious anæmia and the other megaloblastic anæmias, and we suggest that the fundamental difference lies in the precipitating causes—whether achlorhydria, dietary imbalance, other unknown factors, or a combination of all. The term macrocytic used alone is not satisfactory, and is not synonymous with megaloblastic. Macrocytic anæmias can occur that are not megaloblastic, and megaloblastic anæmias that are not macrocytic. We suggest therefore that anæmias be classified according as to whether they have dyshæmopoietic marrows or not, and the terms macrocytic, normocytic, or microcytic added according to cell dimensions.

It is well known that bacterial synthesis of various essential hæmopoietic substances takes place in the alimentary canal (Dyke et al. 1950), and that the administration of antibiotics has a profound qualitative and quantitative effect on the microflora (Bloomfield 1951), destroying or modifying some, facilitating the multiplication of others, changing their amino-acid metabolism (Gale and Taylor 1946, 1947, Paine 1951), blocking part of the Krebs cycle (Van Meter and Oleson 1951), or interfering with oxidative phosphorylisation processes (Lomis 1950, Johnson et al. 1950).

It has also been established that some of the antibiotics, such as aureomycin, may have a sparing effect on vitamin B_{12} and other vitamins (Biely and March 1951). Tentori and Vivaldi (1951) have further shown that the administration of some antibiotics can produce a deficiency of such essential factors as folic acid. The effects of folic acid can be inhibited by such substances as aminopterin and the insoluble sulphonamides. The antagonistic effects of aminopterin can be overcome by either citrovorum factor or aureomycin. The "antagonistic" effects of phthalylsulphathiazole can only be overcome by citrovorum factor, not by antibiotics (Waisman 1952). It is suggested that antibiotics are ineffective after phthalysulphathiazole on account of their known action on intestinal flora. Recent work of our own (in the press) indicates that penicillin is ineffective in the megaloblastic anæmias if insoluble sulphonamides have been given previously.

Hunter (1909) held that the remissions and relapses in pernicious anæmia were due to changes in the bacterial content of the gut. Later Seyderhelm et al. (1924) suggested that an abnormal bacterial flora was responsible for the anæmia that developed in dogs as a result of fibrous stricture of the ileum. Barker and Hummel (1939) thought that the anæmia which develops in cases of intestinal stricture was due to stagnation and putrefaction associated with the absorption of toxins. Cameron et al. (1949a and b, 1950) and Watson et al. (1948) have shown that a megaloblastic ane… a result of the operative production of a … cul-de-sac, and Toon and Wangensteen (1950) and others have shown that this anæmia can …vented or cured by the … of … …hley

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Roine and Elvehjem (1950) have shown that the growth of guineapigs can be greatly improved by adding to the diet a mixture of gum-arabic, potassium acetate, and magnesium oxide, and they conclude that the improvement is due to a change in the intestinal flora.

The complications that often occur during the administration of antibiotics have also been found to be due to drastic changes in the intestinal flora, which may lead to a suppression of the "sensitive" competing flora and to an alteration in the less sensitive synthesising flora (*Lancet* 1952). Serious deficiencies of vitamin-B complex may also occur during the administration of the "wide-spectrum" antibiotics, unless vitamins are given during treatment.

These facts make it very probable that the responses that we have been getting to penicillin in the megaloblastic anæmias are due to changes in the microflora caused by the antibiotics. These changes affect the synthesis and utilisation of essential factors.

There is, we believe, a need to reconsider the intestinal environment in relation to the dyshæmopoietic anæmias and other deficiency states associated with dietary imbalance.

How these findings can be fitted into the intrinsic-extrinsic-factor hypothesis of Castle is not at present clear.

SUMMARY

The megaloblastic anæmias which respond to intramuscular penicillin also respond to oral penicillin.

Alike with oral and with intramuscular penicillin, there seems to be an optimum dose above and below which no response can be obtained. In the cases investigated the optimum dose seemed to be 200,000 units daily for oral penicillin and 400,000 units daily for intramuscular.

Penicillin probably produces its effect by changing the intestinal microflora.

Large doses of penicillin destroy not only the competing flora but also the synthesising flora.

It is suggested that a low-protein high-carbohydrate diet produces a microflora inimical to the synthesis and/or utilisation of hæmopoietic factors. This may explain why the incidence of deficiency states related to vitamin-B complex are so common in Africa, India, and the Balkans.

Our thanks are due to the Director of Medical Services, Kenya, for permission to publish this paper. We are most grateful to Dr. T. A. Henry and Dr. J. L. Winteler for putting us into touch with cases 2 and 4; to Dr. Geoffrey Timms, director of the Medical Research Laboratories, for innumerable facilities and help, without which most of this work would have been impossible; and the doctors and nurses of King George VI Hospital, Nairobi.

REFERENCES

Aitken, M. A., Badenoch, J., Spray, G. H. (1950) *Brit. J. exp. Path.* 31, 355.
Allen, G., Critchley, C. F. (1951) *Brit. med. J.* i, 677.
Barker, W. H., Hummel, L. E. (1939) *Bull. Johns Hopk. Hosp.* 64, 215.
Biely, J., March, B. (1951) *Science*, 114, 330.
Bloomfield, A. L. (1951) *Arch. intern. Med.* 88, 135.
Cameron, D. G., Callender, S. T. E., Watson, G. M., Witts, L. J. (1949a) *Nature, Lond.* 164, 188.
— Watson, G. M., Witts, L. J. (1949b) *Blood*, 4, 803.
— — — (1950) *Brit. J. exp. Path.* 31, 349.
Dyke, W. J. C., Hind, H. G., Riding, D., Shaw, G. E. (1950) *Lancet*, i, 486.
Foy, H., Kondi, A., Hargreaves, A. (1951) *Brit. med. J.* i, 380, 1108.
Gale, E. F., Taylor, E. S. (1946) *Nature, Lond.* 158, 676.
— — (1947) *J. gen. Microbiol.* 1, 77.
Hunter, W. (1909) Severest Anæmias. London.
Johnson, R. B., Feldott, G., Lardy, H. A. (1950) *Arch. Biochem.* 28, 317.
Lancet (1952) i, 352.
Lomis, W. F. (1950) *Science*, 111, 474.
Paine, T. F. jun. (1951) *J. Bact.* 61, 259.
Roine, P., Elvehjem, C. A. (1950) *Proc. Soc. exp. Biol., N.Y.* 73, 308.
Seyderhelm, R., Lehmann, W., Wichels, P. (1924) *Klin. Wschr.* 3, 1439.
Tentori, L., Vivaldi, G. (1951) *Proc. Soc. exp. Biol., N.Y.* 78, 375.
Toon, R. W., Wangensteen, O. H. (1950) *Ibid*, 75, 762.
Ungley, C. G. (1951) See *Lancet*, ii, 1068.
Van Meter, J. C., Oleson, J. J. (1951) *Science*, 113, 273.
Waisman, H. (1952) *Blood*, 7, 172.
Watson, G. M., Cameron, D. G., Witts, L. J. (1948) *Lancet*, ii, 404.

SUCCINYLCHOLINE (SUCCINOYLCHOLINE)

MUSCLE-RELAXANT OF SHORT ACTION

J. G. BOURNE
M.A., M.B. Camb., D.A.
CONSULTANT ANÆSTHETIST TO ST. THOMAS'S HOSPITAL, LONDON, AND SALISBURY HOSPITAL GROUP

H. O. J. COLLIER
B.A., Ph.D. Camb.
CHIEF PHARMACOLOGIST, RESEARCH DIVISION, ALLEN & HANBURYS LTD., WARE, HERTS

G. F. SOMERS
B.Sc., Ph.D. Lond.
LECTURER IN PHARMACOLOGY, SCHOOL OF PHARMACY, UNIVERSITY OF LONDON

A DRUG capable of giving, in the anæsthetised patient, a brief but complete muscular relaxation is required for intubation, electroconvulsive therapy, orthopædic manipulation, and other purposes. The very short duration of action of succinylcholine (succinoylcholine) in experiments on laboratory animals, and its other pharmacological properties, suggested that it might fulfil this need.

Chemistry

Succinylcholine was synthesised first by Hunt and Taveau (1911) and later by Glick (1941), who showed that it was readily hydrolysed both by the esterase of horse-serum and by alkali. Bovet et al. (1949) first demonstrated its powerful neuromuscular blocking activity, which was independently described in this country by Buttle and Zaimis (1949), using material synthesised by Walker (1950). In the United States it was synthesised by Phillips (1949), and its pharmacology was studied by Castillo and de Beer (1950).

Succinylcholine chloride, which was largely used in the clinical studies reported here, is a white solid, crystallising with two molecules of water. The melting-point of the dihydrate is 157°C (Taylor 1952). It is very readily soluble in water to give a slightly acid solution. Biological tests have shown that succinylcholine is stable in acid but rapidly hydrolysed in alkaline solutions.

Pharmacology

MODE OF ACTION AND RELATION TO OTHER DRUGS

In its actions and its relations to other drugs succinylcholine resembles decamethonium and differs from *d*-tubocurarine. Buttle and Zaimis (1949), for example, have shown that both succinylcholine and decamethonium cause spastic paralysis when injected into chicks, whereas true curarising drugs, such as *d*-tubocurarine and gallamine triethiodide ('Flaxedil'), cause flaccid paralysis. Both succinylcholine (Bovet et al. 1949, Ginzel et al. 1951) and decamethonium (Paton and Zaimis 1949) cause contracture of amphibian muscle, though *d*-tubocurarine does not. Succinylcholine, like decamethonium and unlike *d*-tubocurarine, first stimulates the contraction of mammalian muscle before depressing it (Ginzel et al. 1951, Somers 1951). As with decamethonium, antagonism exists between succinylcholine and curare-like drugs (Bovet et al. 1951). Thus, succinylcholine, administered to the cat during recovery from true curarisation, hastens that recovery (Collier and Macauley 1952).

Though succinylcholine resembles decamethonium in its mode of action, it differs from decamethonium in being destroyed by cholinesterases. It is broken down, in-
both by the "pseudo"-cholinesterase of
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Since succinylcholine is destroyed by cholinesterases, neostigmine and other drugs that inhibit cholinesterases prolong the action of succinylcholine (Bovet et al. 1951, Castillo and de Beer 1950, Somers 1951). Hence, though neostigmine is a useful antidote to *d*-tubocurarine and gallamine, it would be worse than useless and is contra-indicated as an antidote to succinylcholine.

SIDE-EFFECTS OF SUCCINYLCHOLINE

Since succinylcholine resembles acetylcholine in chemical structure and in depolarising action on the motor end-plate, we might expect that others of its pharmacological effects would be related to those of acetylcholine. To some extent this is so; but large doses of succinylcholine are required to produce the side-effects seen.

Succinylcholine in large doses has a "nicotinic" effect on the blood-pressure of anæsthetised animals, similar to that of acetylcholine. Thus in the dog doses of >5 mg. of succinylcholine per kg. body-weight—which is more than 25 times the relaxant dose—cause a rise in blood-pressure (Bovet et al. 1949). In the cat doses of about 10 mg. per kg. body-weight are needed to raise the blood-pressure, and this action is abolished by the administration of the ganglion-blocking agents hexamethonium and tetraethylammonium (Somers 1952). In neither the cat nor the dog have we seen any hypotensive effect of succinylcholine.

That succinylcholine increases the flow of saliva in the dog has been reported by Bovet et al. (1951) and Ginzel et al. (1951). We have been unable to confirm this in the anæsthetised dog or cat, even when very large doses were used. On the other hand, we have confirmed the observation of Bovet and his co-workers that succinylcholine in very high concentrations stimulates the isolated intestine of the rabbit and guineapig.

An undesirable property of *d*-tubocurarine and of gallamine is the blocking of autonomic ganglia. Succinylcholine does not appear to block them (Bovet et al. 1949). We have confirmed this in vitro, using the technique described by Collier and Macauley (1952).

A further undesirable property of existing curarising agents is the release of histamine. To investigate this we experimented with intradermal injection in man, using the method described by Collier and Macauley (1952). These experiments showed that succinylcholine was a very weak histamine-liberator, having about a hundredth of the activity of *d*-tubocurarine.

The toxicity of repeated doses of succinylcholine has been studied in rabbits. For 5 successive days 5 rabbits were given a daily intravenous body-weight, which was enough but to kill none. These animals under observation for 8 weeks toxic effects being manifest.

The freedom of succinylcholine indicated by some experiments in Bovet et al. (1951). Dogs whose r tained in an iron lung tolerated a do that is 450 times the paralysing dose, not tolerate more than 15 times the *d*-tubocurarine.

Clinical Application

Succinylcholine has been *administe* adventure to 546 patients, ranging in a years, for the following procedures:

Procedure
Intubation .. ..
Electroconvulsive therapy .. .. ..
Abdominal relaxation .. ..
Œsophagoscopy .. ..
Orthopædic manipulation .. .. ..
Bronchoscopy .. ..
Miscellaneous .. ..
Total .. ..

Doses have ranged from 5 to 300 mg. in single and up to 2300 mg. has been given by intrav continued for three hours.

While these studies were in progress, we l the experience of some Continental anæsthet succinylcholine. After a preliminary trial by (1951), Von Dardel and Thesleff (1951a) reported in 132, and later (1951b) in 1000, *operations*; Holmberg and Thesleff (1951) described its use in e convulsive therapy. These workers found *that relax was satisfactory and the compound had no toxic ef* The clinical use of succinylcholine was also reporte Brücke et al. (1951), who gave it to 17 patients with ill effect.

METHODS

Narcosis

In the work recorded here succinylcholine has always been used in conjunction with an anæsthetic. For long operations thiopentone supplemented with nitrous oxide and oxygen was used, as described by Brennan (1952). For short procedures thiopentone alone was used, with oxygen. The maximal dose of thiopentone was 5 mg. per lb. (11 mg. per kg.)

For patients receiving nitrous oxide the flow-rate was 6 litres per minute (75%) with oxygen 2 litres per minute (25%). A low concentration of trichloroethylene was sometimes used to lessen the chance of coughing.

Premedication was light, except in children. No adult received more than papaveretum ('Omnopon') gr. $^1/_6$ with scopolamine gr. $^1/_{150}$; but all the children were given these drugs in half these doses. A few patients were given pethidine.

Muscular Relaxation

Succinylcholine chloride ('Scoline') was given intravenously. A 5% solution was used; and the usual dose of this expressed in ml. was a hundredth of the body-weight in lb. (1·1 mg. per kg.). Thus, for a man weighing 160 lb. it was 1·6 ml. (80 mg.). For electro-convulsive therapy the dose was half this. These doses are safe, but smaller ones were often found satisfactory.

ACTIONS OF SUCCINYLCHOLINE IN MAN

Preliminary Contractions

The first visible effects of injection of succinylcholine were diffuse uncoördinated contractions of muscle bundles

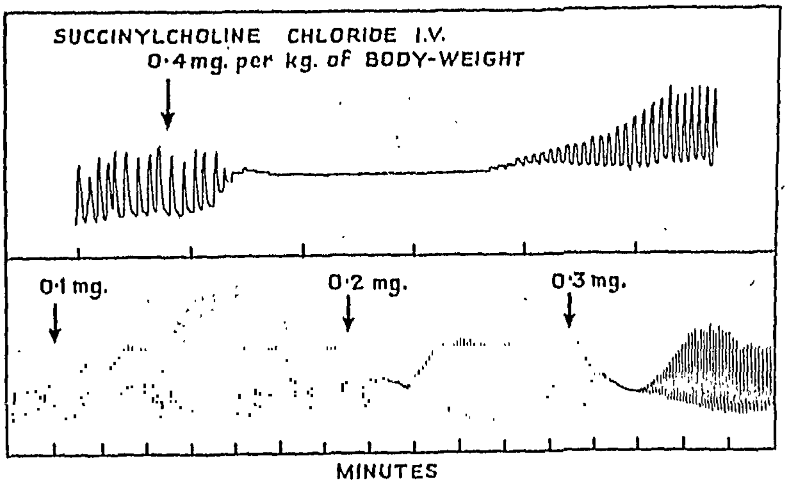


Fig. 1—Spirometer tracings showing effect of succinylcholine on respiration of healthy male weighing 11 st. (70 kg.), during light cyclopropane anæsthesia for herniorrhaphy. Upper tracing fast drum, showing characteristically transient "rectangular" pattern during recovery. Lower tracing: slow drum.

These were seen in adults 12–15 seconds, en as soon as 7 seconds, after injection. al vigour of these contractions may se of succinylcholine unwise in certain may give rise to a feeling of muscular r consciousness has been regained. In volunteer these contractions were painful, contra-indicates the use of succinylcholine has been previously induced; and, since these come on more quickly than thiopentone the two drugs should not be mixed in one

ffect

tractions caused by succinylcholine lasted onds, and their disappearance indicated the aralysis. In the great majority of patients this lasted 2–6 minutes; muscle power then began and was normal in a further 3 or 4 minutes. doses than the one indicated above produced nsient, and larger doses longer, paralysis. ive doses always caused respiratory arrest. s counteracted in short procedures by inflating gs with oxygen. During longer operations artificial tion was continued with the nitrous oxide/oxygen mixture. Excessive artificial respiration, which would lead to acapnia, was avoided. The effect of succinylcholine on respiration and the transience of its action are both clearly shown in the spirometer tracings (fig. 1) which were kindly provided by Dr. H. J. V. Morton.

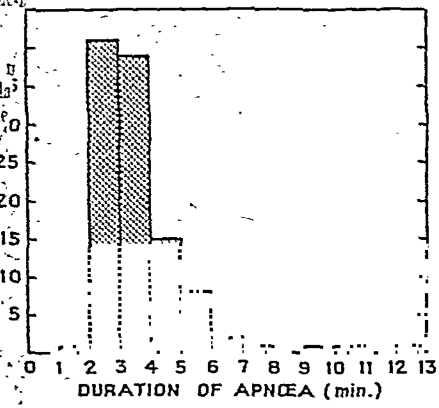


Fig. 2—Distribution of duration of apnœa in 110 patients after succinylcholine 1·1 mg. per kg. body-weight.

In 7 patients hexamethonium or pentamethonium was administered in addition to succinylcholine. With doses of 30–100 mg. of the hypotensive drug no alteration in the patient's reaction to succinylcholine was noticed.

Prolonged Action

Gould (1952), Love (1952), Harper (1952), and Hewer (1952) have reported cases of very prolonged apnœa following a clinical dose of succinylcholine. In our series of 546 patients we found only 5 in whom apnœa was prolonged beyond 8 minutes, and in none did it last more than 15 minutes. In 110 patients the duration of apnœa after a dose of succinylcholine 1·1 mg. per kg. body-weight was timed as accurately as possible. The distribution of its duration is illustrated in fig. 2.

Since it has been reported that succinylcholine is destroyed by cholinesterases, their concentrations in the bloods of 6 patients showing recovery delayed beyond 8 minutes were estimated through the kindness of Mr. D. R. Davies. At the same time the blood-esterase levels of 6 patients who recovered with normal rapidity from succinylcholine were also estimated. In all the patients the cell-cholinesterase levels were normal. The mean plasma-cholinesterase levels and their standard errors, expressed in the units of Callaway et al. (1951), were: delayed recovery patients 38·3 ± 6·8 units; normal recovery patients 88·5 ± 6·9 units. Those patients who recovered unusually slowly from succinylcholine had therefore significantly lower plasma-cholineste than did patients who recovered at the nor ($P<0{\cdot}01$).

The mean plasma-cholinesterase level in who recovered normally from succinylcholine to the mean value obtained by Callaway et al. 247 healthy adults, while the mean for patients delayed recovery lies close to the lower limit in the series of subjects. In certain apparently normal pers (Davies 1952) and in certain conditions, such as insecticide poisoning (Barnes and Davies 1951), liver disease, and malnutrition, plasma-cholinesterase levels may be depressed below normal limits. In these conditions we might perhaps expect recovery from succinylcholine to be unduly delayed. Where this possibility exists it may be advisable to use smaller doses than in the present work.

Side-effects

Succinylcholine was remarkably free from side-effects when given in normal clinical doses. No rise in blood-pressure was seen when single doses were used. When large doses were given by intravenous drip, however, the blood-pressure rose steadily. An electrocardiogram of one patient receiving a single dose of 300 mg. of succinylcholine showed no abnormalities other than an increase in the height of the T-wave from 2 to 4 mm.

In experiments on salivation 5 patients were premedicated with papaveretum alone. In these the usual dose of succinylcholine did not increase the secretion of either saliva or mucus. A 6th patient received no premedication and was given 200 mg. of succinylcholine and 15 minutes later 225 mg. In this patient also no increase in secretions was observed. In patients who had not had atropine or scopolamine, however, copious secretions followed the insertion of instruments into the mouth and pharynx.

USES

Intubation

The use of *d*-tubocurarine for intubation, with thiopentone nitrous oxide/oxygen anæsthesia, was described by one of us in 1947 (Bourne 1947). Since then gallamine and decamethonium have been used for the same purpose, but all three relaxants possess the disadvantage of long action. The prompt and complete paralysis produced by succinylcholine, followed by rapid recovery, made this relaxant ideal for intubation.

After the administration of thiopentone and succinylcholine the lungs were inflated with oxygen. To control coughing, the larynx was then sprayed both above and below the vocal cords with a surface anæsthetic delivered from a Macintosh spray. In tonsillectomy and dental operations the gag or prop was inserted before the action of the relaxant wore off. After intubation succinylcholine was sometimes supplemented by a long-acting relaxant.

With succinylcholine after very small doses of thiopentone, or after induction with cyclopropane, endotracheal anæsthesia could be induced, and the pharynx packed, in the outpatient department. In this way difficult dental extractions could be safely done in the casualty department, saving beds and expense.

Laryngoscopy

Mr. W. A. Mill has drawn our attention to the help given by a no. 7 nasotracheal tube in laryngoscopy and biopsy of lesions in the region of the anterior commissure. The tube lies in the posterior part of the glottis and holds the vocal cords apart. When laryngoscopy was performed in this manner, the anæsthetist had control of respiration and could use succinylcholine; but without such a tube it was better to use a long-acting relaxant in subparalysing dose.

Bronchoscopy

The use of succinylcholine in bronchoscopy proved difficult, since the patient passed too rapidly between the extremes of paralysis and strength. Here, gallamine

Since suc pentone was preferred. But, provided the
neostigmine well inflated beforehand with oxygen, the
prolong the inylcholine in bronchoscopy was satisfactory
Castillo and xamination was brief or the surgeon permitted
neostigmin ns for reinflation.
gallamine scopy
indicate a nasotracheal tube gave full control of respira-
, and after the initial injection of thiopentone narcosis
as continued with nitrous oxide/oxygen. Repeated
injections of 50 or 100 mg. of succinylcholine were given to maintain paralysis until the examination was finished. Artificial respiration with the gas mixture was continued until the patient had recovered his strength.

Electroconvulsive Therapy

Patients were instructed not to eat before coming for treatment. To prevent excessive salivation, sometimes caused by convulsion therapy, atropine gr. $^1/_{50}$ was given subcutaneously half an hour before treatment. Immediately before treatment thiopentone was given intravenously, followed by succinylcholine from a different syringe but through the same needle. The lungs were then inflated with oxygen for one minute and the convulsion induced.

Large doses of succinylcholine were found to paralyse the patient so deeply that no convulsions were seen; but, when the dose in millilitres of a 5% solution of thiopentone was equivalent to a thirtieth, and that of a 5% solution of succinylcholine to a two-hundredth, of the body-weight in pounds, the effects of the shock were well modified but not masked.

Other Short Procedures

Succinylcholine has been found valuable in laryngeal spasm, in hiccup, in orthopædic manipulations, in closure of the abdomen when relaxation with curare or gallamine was wearing off, and in examinations under anæsthesia. It was also useful in overcoming a severe trismus in a labourer lightly anæsthetised with cyclopropane in the casualty department for extraction of a septic molar tooth.

Abdominal Relaxation

Succinylcholine has been applied to abdominal surgery in four different ways:

(1) Succinylcholine has been used to supplement curare or gallamine, given both before them for intubation and at the end for closing the abdomen when their effect was wearing off. Used at the end for sewing up, it obviated the need for additional doses of gallamine or curare, and made the use of their antidote, *neostigmine*, less often necessary. When the succinylcholine has worn off, if there remains any doubt whether the patient has sufficiently recovered from the curare or gallamine, neostigmine should be given even in a full 5 mg. dose.

(2) Succinylcholine has been successfully used to supplement decamethonium in some old and bronchitic patients, where it was thought inadvisable to give neostigmine, because of its action on bronchial secretion.

(3) Succinylcholine was used as the sole relaxant and given by frequently repeated injections, as in the following case:

Case 1.—Man, aged 64; weight 160 lb.; Millin's prostatectomy.

2.55 P.M. Thiopentone 5% (10 ml.). Inflation with oxygen.
2.58 P.M. Succinylcholine 100 mg. (2 ml.). Intubation and inflation with nitrous oxide/oxygen.
3.02 P.M. Adequate spontaneous respiration.
3.03 P.M. *Succinylcholine 200 mg. (4 ml.).*
3.10 P.M. Adequate spontaneous respiration.
3.12 P.M. Succinylcholine 300 mg. (6 ml.).
3.20 P.M. Spontaneous respiration of "rectangular" type.
3.23 P.M. Vigorous breathing and coughing. Pethidine 50 mg. intravenously and patient left breathing nitrous oxide/oxygen.
3.50 P.M. Patient transferred to theatre.
3.53 P.M. Coughing vigorously.
3.56 P.M. Succinylcholine 100 mg.
3.58 P.M. Succinylcholine 50 mg. Gentle artificial respiration
with gas and oxygen ach time
feeble spontaneous succinyl-
choline 50 mg. was g striking
regularity every 3 n hen the
operation was complete.

4.36 P.M. *Spontaneous respiratio* n reappeared.
4.37 P.M. Respiration just "ado uate."
4.39 P.M. Respiration strong and deep.

This patient received in all 13 —50 mg. of succinylcholine.
The duration of relaxation after ea ers, th dose of 50 mg. remained
remarkably constant; there was n into o evidence of cumulative
effect or tolerance; and final recover ital fe y of power was quick and
complete.
ticulo
trength after injection

In case 2 recovery of muscular s llustra
of succinylcholine was less rapid: o imp

Case 2.—Woman, aged 63; 90 l y, wh b.; acute intestinal
obstruction. She had had intestinal ol to ch struction for fifteen
days. A single dose of succinylcholine 50 d the mg. caused complete
paralysis for 10 minutes. After a further dose of 60 mg. she
remained detectably weakened for 23 m e gast inutes, during the
first 15 of which respiration was paralysed. the

(4) Succinylcholine was given as so hich le relaxant by
continuous intravenous infusion in salin s be e solution.

Case 3.—Woman, aged 38; 140 lb.; ch ecor olecystectomy.
Anæsthesia was induced with 14 ml. 5% th na iopentone and
continued with nitrous oxide/oxygen with c h arbon dioxide
absorption and "controlled" respiration. Ve di ntilation was
regulated so as to avoid either anoxia or acapn ic
5% succinylcholine was given for intubation, and
was then maintained by infusion of a 0·67% solutio
rate of 25 drops (equivalent to 10–11 mg.) *per minut*
patient in a state of relaxation, in which spontaneou
tion was just visible on the breathing bag. The
received in 80 minutes 950 mg. of succinylcholine.
was stopped when the peritoneum was being closed, a
moment spontaneous respiration was just detectable.
breathing then rapidly improved and 5 minutes late
adequate. At 7 minutes after stopping the drip the pa
coughed; and at 9 minutes she was coughing and breat
strongly.

In this case recovery of strength took rather long than expected. This delay in recovery was a feature case 4:

Case 4.—Man, aged 58; 219 lb.; partial gastrectomy. Induction and maintenance of anæsthesia and infusion of succinylcholine was as in case 3. The relaxant was infused at a rate of about 12 mg. a minute during three hours of the operation (total 2300 mg.). During the first hour spontaneous respiration was just visible, but thereafter it was absent. At 4 minutes after stopping the drip spontaneous respiration returned. Thenceforward recovery of strength was slow. At 16 minutes breathing was stronger but still "rectangular" (as exemplified in fig. 2) and inadequate, with tracheal tug. At 20 minutes nitrous oxide/oxygen narcosis was stopped. At 23 minutes the patient was able to move feebly. At 33 minutes he was talking, but unable to phonate, and was still very weak. At 38 minutes he had no hand-grip and could not raise his head from the table. At 48 minutes he was returned to the ward, but he did not recover his full strength for a further hour. Thenceforward his recovery and convalescence were uninterrupted.

In spite of this slow recovery, however, it is noteworthy that such a large dose of succinylcholine had no other untoward effect. In a patient who received 475 mg. of succinylcholine in 36 minutes, no delay in recovery was seen.

Summary

The chemistry and pharmacology of succinylcholine are outlined, and its use in 546 patients is described. It is a safe and effective muscle-relaxant, particularly valuable in short procedures such as intubation, electroconvulsive therapy, and orthopædic manipulation. It may also be used to supplement relaxation when the effects of a long-acting relaxant are waning. In doses required for such procedures it is remarkably free from side-effects.

Succinylcholine is generally very short in its period of action. In all but a few patients the relaxant effect of a single dose, judged by the duration of apnœa, did not exceed 8 minutes. In a few people it exceeded 8 but not 15 minutes. The bloods of 6 persons who recovered abnormally slowly were examined and showed low plasma-cholinesterase levels.

long operations succinylcholine has been given either by repeated injections or by continuous venous drip. In spite of the satisfactory experience m Dardel and Thesleff (1951a), who used lower doses, onsider that long-continued infusion of heavy doses ccinylcholine may have disadvantages, such as a ly rise in blood-pressure and a delay in recovery. also cumbersome.

should like to thank Dr. H. J. V. Morton for the tracings nted in fig. 1; Mr. D. R. Davies for cholinesterase tions; and Messrs. Allen & Hanburys Ltd. for supplies inylcholine chloride ('Scoline').

REFERENCES

J. M., Davies, D. R. (1951) *Brit. med. J.* ii, 816.
J. G. (1947) *Ibid*, ii, 654.
D., Bovet-Nitti, F., Guarino, S., Longo, V. G., Fusco, R. 51) *Arch. int. Pharmacodyn.* 88, 1.
— — Marotta, M. (1949) *R.C. Ist. sup. Sanità*, 12,
itti, F. (1949) *Ibid*, p. 138.
, H. J. (1952) *Anæsthesia*, 7, 27.
H., Ginzel, K. H., Klupp, H., Pfaffenschlager, F., Werner, G. 51) *Wien. klin. Wschr.* 63, 464.
G. A. H., Zaimis, E. J. (1949) *J. Pharm. Pharmacol.* 1, 991.
y, S., Davies, D. R., Rutland, J. P. (1951) *Brit. med. J.* 812.
J. C., de Beer, E. J. (1950) *J. Pharmacol.* 99, 458.
H. O. J., Macauley, B. (1952) *Brit. J. Pharmacol* (in the ss).
D. R. (1952) Personal communication.
K. H., Klupp, H., Werner, G. (1951) *Arch. int. Pharmacodyn.* 79.
D. (1941) *J. biol. Chem.* 137, 357.
R. B. (1952) *Brit. med. J.* i, 440.
r, J. K. (1952) *Ibid*, p. 866.
r, C. L. (1952) *Ibid*, p. 971.
berg, G., Thesleff, S. (1951) *Nord. Med.* 46, 1567.
R., Taveau, R. (1911) *Publ. Hlth marine Hosp. Service, U.S.A., hyg. Lab. Bull.* no. 73.
, S. H. S. (1952) *Anæsthesia*, 7, 113.
n, W. D. M., Zaimis, E. J. (1949) *Brit. J. Pharmacol.* 4, 381.
ips, A. P. (1949) *J. Amer. chem. Soc.* 71, 3264.
rs, G. F. (1951) Communication to British Pharmacological Society, Sheffield, July.
(1952) In preparation.
or, G. P. (1952) Personal communication.
S. (1951) *Nord. Med.* 46, 1045.
rdel, O., Thesleff, S. (1951a) *Ibid*, p. 1308.
— (1951b) Communication to 26th Int. Congr. Anæsthesiol. ondon, September.
er, J. (1950) *J. Chem. Soc.* p. 193.

NSITIVITY TO SUCCINYLCHOLINE IN LATION TO SERUM-CHOLINESTERASE

F. T. EVANS
M.B. Lond., M.R.C.P., F.F.A. R.C.S.
ANÆSTHETIST

P. W. S. GRAY
M.B. Lond., D.A.
SENIOR REGISTRAR IN THE DEPARTMENT OF ANÆSTHESIA

H. LEHMANN
M.D. Basle, Ph.D. Camb., F.R.I.C.
SENIOR LECTURER IN CHEMICAL PATHOLOGY

E. SILK
B.Sc. Lond.
RESEARCH ASSISTANT

ST. BARTHOLOMEW'S HOSPITAL, LONDON

MUCH interest has been taken in recent years in the thonium compounds in general, and, as far as anæs-sia is concerned, in the short-acting muscle relaxants which two choline groups are linked to succinic acid. Succinylcholine (succinoylcholine) is injected to give ef muscular relaxation in intubation, manipulation, d in electroconvulsion therapy. Disturbing reports ve appeared about this drug. Hurley and Monro 952) had a patient in whom paralysis lasted for 10 inutes; Langton Hewer (1952) observed an effect lasting 42 minutes; Love (1952) reported on two patients who did not recover for 20 minutes, and one in whom the effect lasted a full hour; and Harper (1952) described response lasting three hours.

In our experience with more than four hundred patients the response usually lasts from 2 to 4 minutes, ut in two patients we saw recently it lasted 20 and 21 minutes.

It has been known since 1949 that succinylcholine is destroyed by rabbit cholinesterase (Bovet et al. 1949, Bovet-Nitti 1949). This makes it likely that its short action is the result of rapid destruction by an enzyme in the human blood. We thought that, if this was so, the alarming reactions might be related to low cholinesterase levels in these patients' red cells or serum. We therefore studied the enzymic hydrolysis of succinylcholine in vitro and measured the serum-esterase level in four people who showed a normal reaction to the drug, and in the two patients whose response was prolonged.

TABLE I—SUCCINYLCHOLINE BREAKDOWN BY RED-CELL AND SERUM ESTERASES AND ITS EFFECT ON ACETYLCHOLINE HYDROLYSIS

µl. CO_2 liberated per ml. serum or packed red cells per min. at 37°C

Substrate	Acetyl-choline	Succinyl-choline	Acetyl-choline + succinyl-choline
Serum "pseudo"-cholinesterase			
Acetylcholine: 8 mg. per ml.	58	4	2
Succinylcholine: 16 mg. per ml.	92	5	75
Red-cell (true) acetylcholinesterase			
Acetylcholine: 0·8 mg. per ml.	59	0	20
Succinylcholine: 1·6 mg. per ml.	147	0	43

METHODS

The succinylcholine used was the preparation made by Allen & Hanburys Ltd. ('Scoline'). The amounts of acetylcholine mentioned below refer to the monochloride salts respectively, those of succinylcholine to the dichloride. The esterase activity was measured in the Warburg micromanometer (Jones and Tod 1935) following exactly the technique of McArdle (1940) which depends on the evolution of CO_2 from a bicarbonate buffer by the products of esterhydrolysis. The activity of the enzyme solutions is expressed as µl. of CO_2 formed per minute by 1 ml. of serum or packed red cells at 37°C.

The "pseudo"-acetylcholinesterase was measured using serum in a final dilution of 1/15, with 8 mg. acetylcholine per ml., and the true acetylcholinesterase was determined using a final 1/75 dilution of packed, washed, and hæmolysed red cells with 0·8 mg. per ml. of acetylcholine as substrate. The succinylcholine concentrations are given below. Controls for non-enzymic destruction of esters were included in all experiments.

RESULTS

Blood contains two cholinesterases; one—unspecific as far as acetylcholine is concerned—is the "pseudo"-acetylcholinesterase of the serum, the other is the true acetylcholinesterase of the red cells.

Table I shows how both enzymes were examined for their effect on succinylcholine. Two enzymes of each kind were tested, one with a high and one with a low activity. It will be seen that succinylcholine is not broken down by the true acetylcholinesterase, but that it is metabolised by the "pseudo"-esterase of the serum, though at a slower rate than acetylcholine; and that succinylcholine is a competitive inhibitor of acetylcholine hydrolysis by both the true and the "pseudo"-acetylcholinesterases; but, of the two, the true esterase is more strongly inhibited. The inhibition can in fact still be demonstrated at a concentration of 5 µg. of succinylcholine per ml.

TABLE II—INHIBITION OF SERUM-CHOLINESTERASE BY SUCCINYLCHOLINE

µl. CO_2 liberated per ml. serum per minute at 37°C from 8 mg. acetylcholine per ml.

Succinylcholine µg./ml. ..	0	125	250	500	1000	2000	4000
Esterase activity	55	52	47	41	25	17	15
Inhibition (%)	—	5	15	25	55	69	73

TABLE III—RELATION BETWEEN SERUM-CHOLINESTERASE AND RESPONSE TO SUCCINYLCHOLINE

Sex	Succinylcholine (mg. per lb. body-weight)	Stoppage of breathing (seconds)	Serum-cholinesterase (units)
F	0·32	100	98
F	0·33	125	94
F	0·30	188	63
M	0·40	235	55
M	0·40	1200	12
M	0·50	1260	12

The micromanometric technique cannot measure in vitro the hydrolysis of succinylcholine at concentrations sufficiently low to be comparable with those used in the anæsthesia of patients. Table II shows that with a concentration of 250 µg. per ml.—i.e., when proof of hydrolysis by measurement of CO_2 evolution becomes impossible—combination of the enzyme with succinylcholine can be demonstrated by showing considerable inhibitory action by the ester on enzymatic acetylcholine breakdown. Some action can even be demonstrated at a concentration of 125 µg. per ml., but here the effect is almost within the limits of experimental error.

Table III shows the correlation between the time of relaxation, as measured by the interval before the return of normal breathing, and the serum-esterase level. Thiopentone was given first in all cases, and there was, of course, no paralysis of the respiratory muscles until the succinylcholine was given intravenously. The activity of the serum-acetylcholinesterase is approximately in indirect proportion to the response to the drug—i.e., the product of units of serum-cholinesterase and the duration of response in minutes is about 200. In the patients with an esterase activity of 90–100 units, the response lasted about 2 minutes; at about half that activity the duration was 3–4 minutes; and at about one-tenth of the serum-esterase activity of the first group the paralysis lasted for 20 minutes.

The last two results were obtained in the patients whose response to succinylcholine had been prolonged. In one, the low serum-esterase level was found after the hypersensitivity to the drug had been observed; in the second, the esterase level was known before the operation. To avoid prolonged paralysis of the respiratory muscles, we no longer give succinylcholine to patients who are known to have a low serum-cholinesterase activity. We should be grateful to hear of other patients in whom such a pathological response has been observed, and to have an opportunity of investigating their esterase levels.

DISCUSSION

It is reasonable to assume that succinylcholine acts by inhibiting the true acetylcholinesterase at the neuromuscular junction, and that the removal of the drug by the "pseudo"-cholinesterase of the serum normally curtails its effect. That the target of the drug is the acetylcholinesterase of the nerve-muscle end-plates is supported by the fact that the longest response seen so far is that reported by Harper (1952), when neostigmine was given in addition and when the patient did not recover for three hours.

Both in-vitro and in-vivo observations on the serum-esterase make it likely that its level determines the duration of relaxation. It might, therefore, be wise not to give succinylcholine to patients likely to have a low serum-esterase level, such as may be found in liver disease, severe anæmia, and after poisoning with anti-cholinesterase compounds—e.g., certain agricultural insecticides and war gases. Succinylcholine should certainly not be administered unless facilities are available for prolonged artificial respiration. Should we meet succinylcholine sensitivity unexpectedly in the future, we intend to counteract the paralysis with blood-transfusion or transfusion of fresh plasma.

SUMMARY

In two patients who responded to the standard dose succinylcholine with a paralysis of 20 and 21 minut duration, the "pseudo"-cholinesterase level was foun to be very low.

Succinylcholine was found to be a competitive inhibito of acetylcholine hydrolysis, both by the "pseudo" esterase of the serum and by the true acetylcholinestera of the red cells. The drug itself is hydrolysed only by th "pseudo"-esterase. It is suggested that succinylcholin acts by inhibition of the true acetylcholinesterase at th neuromuscular junction, and that the duration of it effect depends on the speed of its removal by th "pseudo"-cholinesterase of the plasma.

It is a pleasure to thank Mr. A. H. Hunt, on whose patient most of the work was done, for his interest. The work formed part of an investigation of the rôle of cholinesterase in liv disease, an investigation suggested by Dr. B. Mendel, professo of pharmacology in the university of Amsterdam. One of (H. L.) wishes to thank the Halley Stewart Foundation fo a Warburg micromanometric apparatus, and the Medic Research Council for a grant to Mrs. E. Silk, and for defrayin the current expenses incurred in this work.

REFERENCES

Bovet, D., Bovet-Nitti, F., Guarino, S., Longo, V. G., Marotta, (1949) *R. C. Ist. sup. Sanità*, 12, 106; quoted in *Biol. Abstr.* 1950, 24, 32763.
Bovet-Nitti, F. (1949) *R. C. Ist. sup. Sanità*, 12, 138; quoted in *Biol. Abstr.* 1950, 24, 32764.
Harper, J. K. (1952) *Brit. med. J.* i, 866.
Hewer, C. L. (1952) *Ibid*, p. 971.
Hurley, M. J., Monro, A. B. (1952) *Ibid*, p. 1027.
Jones, M. S., Tod, H. (1935) *Biochem. J.* 29, 2242.
Love, S. H. S. (1952) *Anæsthesia*, 7, 113.
McArdle, B. (1940) *Quart. J. Med.* 33, 107.

THE ASSESSMENT OF COUGH-SUPPRESSING DRUGS

B. R. HILLIS
M.D. Glasg., F.R.F.P.S.
ASSISTANT, DEPARTMENT OF MATERIA MEDICA A D THERAPEUTICS IN THE UNIVERSITY OF GLASGOW; REGISTRAR, STOBHILL GENERAL HOSPITAL, GLASGOW

> "I have been hindered by a vexatious and incess cough for which within these ten days I have been bl once, fasted four or five times, taken physick five tim and opiates, I think, six. This day it seems to remit."
>
> —BOSWELL: *Life of Samuel Johnson*

THE essential purpose of coughing is to clear the respiratory tract of an irritant—usually excessive secretion. The reflex thus provides invaluable protection to the air-passages, but there are occasions when the very ease with which it can be provoked proves a serious disadvantage to the patient. A brief spell of forceful coughing is often desirable, but in some cases of respiratory disease coughing often outlives its usefulness. It may damage the mucosa of the upper respiratory tract, and the focus of irritation thus produced may become a secondary cause of intractable coughing. Among the possible complications of persistent coughing the commonest and most distressing are physical exhaustion, loss of sleep, aggravation of pleuritic pain, and stress incontinence.

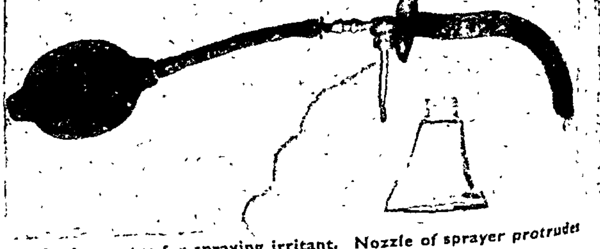


Fig. 1—Apparatus for spraying irritant. Nozzle of sprayer protrudes from anæsthetist's airway for demonstration.

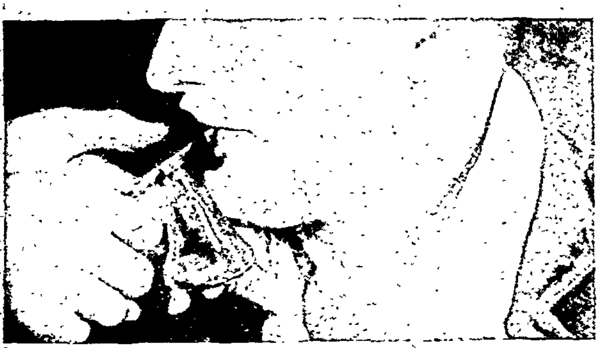


Fig. 2—Apparatus in position for use.

Rational therapeutics aims at eradicating the underlying cause of the cough, but symptomatic treatment is often indicated to give, without delay, some measure of relief. The so-called reflex expectorants are widely used in the hope of increasing the flow of secretion from the bronchial mucosa, but there is no evidence that they act in this way. Patients with chronic bronchitis often discover the soothing effect of sucking sweets, which excites a flow of saliva, thus lubricating the irritable fauces. For alleviating a troublesome cough, however, practitioners depend mainly on the opiates and the synthetic analgesics, which act by depressing the cough centre in the medulla. There can be no doubt about the value of the cough suppressants as a group, but they all suffer, more or less, from the disadvantages of producing undesirable side-effects, such as drowsiness, nausea, and constipation. Further, there is no reliable information, based on objective testing, about the relative merits of drugs of this type. The investigation described below aimed at determining the potency of the cough suppressants in common use.

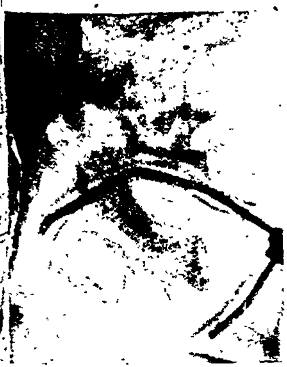


Fig. 3—Radiograph showing end of sprayer behind epiglottis.

PRESENT INVESTIGATION

The first essential was to devise a method for producing artificially, in man, coughs of predictable severity and indistinguishable from the natural cough. A long nasopharyngeal sprayer with a small adjustable nozzle was bent so that it could be inserted over the root of the tongue into the lower pharynx (figs. 1–3). The volunteer who submitted to the long series of tests was a man aged 42. He could tolerate the sprayer in his unanæsthetised pharynx for hours on end, even when the sprayer had been encased in an anæsthetist's airway, which was firmly gripped in the pharynx and kept the sprayer in a constant position. The fact that all the observations were made on one and the same person proved a great advantage in analysing the results, because it disposed of the need to make allowance for variations of susceptibility in different volunteers. At the end of the period of experiment, which lasted nearly a year, careful examination revealed no evidence of any harmful effect in the man's respiratory tract or elsewhere.

Repeated trials showed this to be a reliable method for introducing into the larynx small quantities of fluid sufficiently irritating to precipitate coughing. By varying the stimulant it was possible to evoke at will coughs ranging in severity from threshold level to uncontrollable paroxysms.

In preliminary work the fluids tested included sterile water, physiological saline solution, 2·5% saline, 5% saline, 1/80 peppermint water, 1/40 peppermint water (*B.P.* strength), ether, and trichlorethylene ('Trilene'). Peppermint water (*B.P.*) and ether produced a convenient range of coughs of increasing intensity, and only the results obtained with these preparations are described.

TECHNIQUE

A "trial" means giving successive insufflations, to a maximum of ten, and recording the occurrence or non-occurrence of coughing. The effect of the stimulating agents was determined by making five such "trials" for each irritant in turn before treatment, with suitable intervals to allow recovery from coughing. Thus in the five trials with 1/40 peppermint water the patient might cough at the eighth insufflation in the first trial, and at the sixth, ninth, fifth, and not at all after ten insufflations in the four succeeding trials. When ether was tried, coughs were usually evoked at the first insufflation in four trials, and perhaps at the second insufflation in one trial. An identical number of trials would be repeated after treatment with a supposed cough suppressant, and the results compared. In this manner further sets of trials were repeated on different days, different suppressants being used in random order. The results set out in table I show how the patient responded to insufflations of peppermint water before and after the administration of morphine as a cough suppressant. It is convenient to call this a completed experiment.

TABLE I—MORPHINE AS COUGH SUPPRESSANT

Up to and including	No. of coughs		Index of efficiency
	Before injection	After injection	
1st insufflation	2	0	100
2nd ,,	12	4	67
3rd ,,	20	7	65
4th ,,	25	8	68
5th ,,	27	8	70
6th ,,	31	12	61
7th ,,	31	14	55
8th ,,	32	18	44
9th ,,	33	19	42
10th ,,	34	21	38

An index to express the efficiency of the drug in reducing the number of coughs is obtained by dividing the difference between the number of coughs before and after injection by the number of coughs before injection, and multiplying the result by 100.

Thus if B denotes number of coughs before administration of drug,

And if A denotes number of coughs after administration of drug,

$$\text{Efficiency} = \frac{B-A}{B} \times 100.$$

CONSISTENCY OF STIMULI IN PRODUCING COUGHS

There were unavoidable periods, lasting up to six weeks, during which no experiments could be made, and

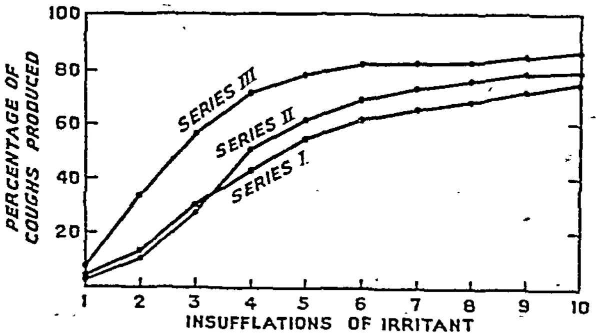


Fig. 4—Percentage of coughs produced with peppermint water.

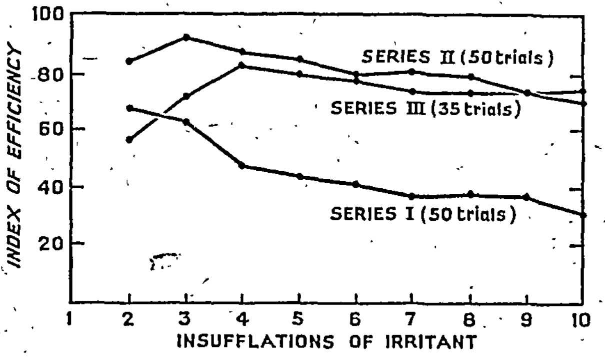


Fig. 5—Apparent efficiency of physiological saline solution in suppressing cough caused by peppermint water.

the complete series has been divided into three smaller series according to the time of the year when the work was done:

Series I, winter 1950–51.
Series II, spring 1951.
Series III, summer 1951.

Although the three series are differentiated by the seasons of the year when the tests were carried out, it is not suggested that the season had any bearing on the results obtained.

Examination of the records of coughs up to and including a given insufflation before administration of the suppressant at different dates was made to determine whether the various agents used evoked coughs in a constant manner. The number of coughs up to and including a given insufflation are divided by the total number of coughs possible (see fig. 4).

TABLE II—APPARENT EFFICIENCY OF HYPODERMIC INJECTION OF SALINE SOLUTION TO SUPPRESS COUGH CAUSED BY ETHER

—	50 trials		
	Series I	Series II	Series III
Index of efficiency of "treatment" at *first* insufflation of irritant	10	38	62

With ether as the stimulant the first insufflation produced a cough in practically all the trials over the three series. These results are consistent and indicate that this technique to evoke cough is reliable.

THE PSYCHOLOGICAL FACTOR

When experiments of this kind are made on man, it is essential to take psychological factors into account. An attempt was therefore made to assess the importance of suggestion by exhibiting inert substances instead of known cough-suppressants. The true potency of these drugs can be determined only by discounting their action appropriately in the light of our knowledge of the effect of placebos under comparable conditions. In these experiments, therefore, an attempt was made to measure the psychological factor by determining the apparent cough-suppressant action of physiological saline solution 1 ml. injected subcutaneously (fig. 5).

TABLE III—APPARENT SUPPRESSION BY SALINE SOLUTION OF COUGHS PRODUCED BY PEPPERMINT WATER

—	No. of trials		
	With coughs	Without coughs	Total
Before injection ..	6	44	50
After injection.. ..	2	48	50
Total	8	92	100

When tested before the administration of opiat &c., ether almost always provoked coughing when t stimulus was minimal—i.e., at the first insufflati (table II). It was therefore decided that, when eth was the irritant, assessments of the cough-suppressa action of drugs and placebos should be restricted to tl phase of the experiment.

The over-all average index of efficiency was near 37, indicating the importance of the factor of suggestio There was no obvious reason for the progressive rise the efficiency of the placebos.

By using a weaker stimulus (peppermint water) tl influence of the psychological factor was determined experiments with larger numbers of insufflations. Tl results (fig. 5) show that suggestion was very importa in the results as a whole, though it tended to dimini as the strength of the stimulus increased.

TABLE IV—SIGNIFICANT DIFFERENCE IN PERCENTAGE COUGHS BEFORE AND AFTER ADMINISTRATION OF SALI SOLUTION

Up to and including	Series I (50 trials)	Series II (50 trials)	Series III (35 trials)
Peppermint water			
2nd insufflation	Not significant	Not significant	Not significa
3rd–10th insufflation ..	Significant	Significant	Significant
Ether			
1st insufflation	Barely significant	Significant	Significant

Significance of Psychological Factor

To find whether the psychological factor caus a significant reduction in the number of coughs, th percentage of coughs before administration of salin solution has been compared with the percentage of cough after administration. The results in series I with peppe mint water up to and including the second insufflatio are shown in table III.

A χ^2 test shows on 5% level of significance that ther is no significant difference in coughs in this instanc

The complete data up to and including a give insufflation give the results shown in table IV.

It is therefore clear that the psychological factor i significant in the person subjected to these experiment and allowance must be made for it by comparing the apparent suppressant action of the drugs with the assessment of the psychological factor present at the time.

TABLE V—PREPARATIONS, DOSES, AND METHODS OF ADMINISTRATION

Series	Drug	Route	Dose	No. of experiments (each of 5 trials)
I, winter	Codeine	Oral	gr. 3	10
	Morphine	Subcut.	gr. 1/4	10
	Heroin	Subcut.	gr. 1/6	10
	Control (saline)	Subcut.	1 ml.	10
II, *spring*	Codeine	Subcut.	gr. 1	10
	Heroin	Subcut.	gr. 1/6	5
	Amidone ('Physeptone')	Subcut.	15 mg.	10
	Control (saline)	Subcut.	1 ml.	10
III, summer	Codeine	Subcut.	gr. 1	7
	Morphine	Subcut.	gr. 1/4	8
	Heroin	Subcut.	gr. 1/6	2
	Amidone	Subcut.	15 mg.	3
	Control (saline)	Subcut.	1 ml.	7

SERIES OF EXPERIMENTS

The series of experiments are shown in table V.

In each series the difference in the number of coughs before and after administration of the drug was determined, and the index of efficiency calculated as described above, up to and including each insufflation (as in table I).

ficiency of Drugs and Control in Reducing Coughs

The results are shown in figs. 6–11. An index of 100 dicates complete elimination of coughing.

At first the efficiency of the drugs in suppressing ughs appears to be high, but it must be discounted by e psychological factor, as assessed by the use of an ert substance. If this factor had remained small, as i the winter series of tests, the effects attributable to rugs would have been more clearly significant, but in e spring and summer series it increased strikingly. t was to minimise this complicating factor of suggestion hat the stronger stimulus of ether was used.

Taken by mouth, codeine gave results which were uch less predictable and consistent than when it was njected subcutaneously. Rather surprisingly morphine lso gave variable results: in the winter series (50 trials) ts cough-suppressant effect decreased with the increasing umber of insufflations of peppermint water, but in the mmer series (40 trials) it had a sustained effect. Again, this winter series the effects of seven to ten insufflations peppermint water were less effectively suppressed than he effect of a single insufflation of ether—which on other ccasions had proved a much stronger stimulus. It is nlikely that the steady decline in efficiency of morphine n the winter series was fortuitous, for the pattern was epeated with ether up to and including the tenth insufflation (see below): but no satisfactory explanation is apparent.

Significance of Apparent Cough-suppressing Action

To find whether there is a significant difference between a drug and the control (physiological saline solution) in their power to reduce coughing, comparisons have been made up to and including each insufflation recorded on the abscissa for the separate irritants (ether and peppermint water) by applying a χ^2 test (cf. table III). An example is given in table VI.

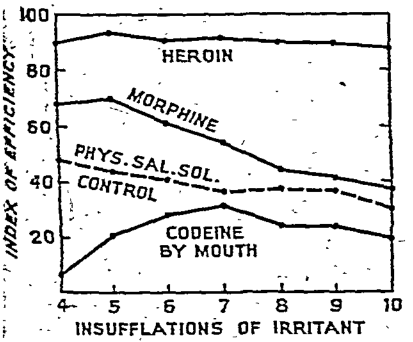


Fig. 6—Efficiency of various drugs in suppressing cough due to peppermint water in series I (50 trials each).

The results obtained in this way for the different substances tested were as follows:

Codeine: oral gr. 3 (180 mg.); subcutaneous gr. 1 (60 mg.).

Oral.—Weak stimulus (50 trials) up to tenth insufflation: no significant difference; strong stimulus (50 trials) at first insufflation: no significant difference.

Subcutaneous.—Weak stimulus (85 trials) up to tenth insufflation: no significant difference: strong stimulus (85 trials) at first insufflation: no significant difference.

Comment.—By this technique codeine did not show a significant difference from the psychological effect, even on parenteral administration.

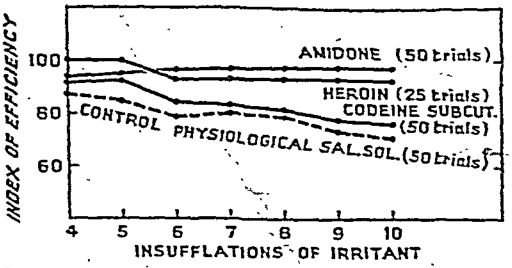


Fig. 7—Efficiency of various drugs in suppressing cough due to peppermint water in series II.

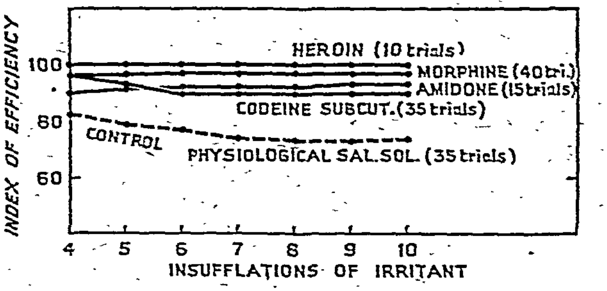


Fig. 8—Efficiency of various drugs in suppressing cough due to peppermint water in series III.

Morphine gr. 1/4 (15 mg.).

Weak stimulus (peppermint water):

Up to and including	*Series I (50 trials)*	*Series III (40 trials)*
3rd insufflation	Not significant	Barely significant
4th ,,	,, ,,	Not significant
5th ,,	,, ,,	,, ,,
6th ,,	,, ,,	,, ,,
7th ,,	,, ,,	Barely significant
8th ,,	,, ,,	,, ,,
9th ,,	,, ,,	,, ,,
10th ,,	,, ,,	,, ,,

Strong stimulus (ether) first insufflation: significant in both series I and III.

Comment.—In the presence of a strong stimulus (ether) the effect of the psychological factor is less apparent, and the action of morphine is such that a definite cough-suppressing action is confirmed in both series.

Amidone gr. 1/4 (15 mg.).

Weak stimulus (peppermint water):

Up to and including	*Series II (50 trials)*	*Series III (15 trials)*
3rd insufflation	Not significant	Not significant
4th ,,	,, ,,	,, ,,
5th ,,	,, ,,	,, ,,
6th ,,	Barely significant	,, ,,
7th ,,	Significant	,, ,,
8th ,,	,,	,, ,,
9th ,,	,,	,, ,,
10th ,,	,,	,, ,,

Strong stimulus (ether) first insufflation: significant in series II and barely significant in series III.

Comment.—In a small series of trials (series III) the high psychological factor cannot be dissociated sufficiently from the cough-suppressing effect. In a large number of trials, however, a significant difference is obtained, even in the upper range of the weaker stimulus.

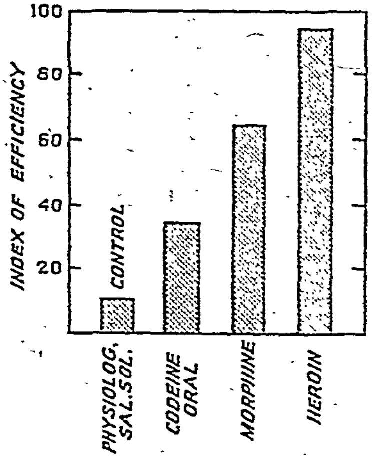


Fig. 9—Efficiency of various drugs in suppressing cough due to 1st insufflation with ether in series I (50 trials each).

Heroin gr. 1/6 (10 mg.).

Weak stimulus (peppermint water):

Up to and including	*Series I (50 trials)*	*Series II (25 trials)*	*Series III (10 trials)*
3rd insufflation	Not significant	Not significant	—
4th ,,	Significant	,, ,,	Not significant
5th ,,	,,	,, ,,	,, ,,
6th ,,	,,	,, ,,	,, ,,
7th ,,	,,	,, ,,	,, ,,
8th ,,	,,	,, ,,	,, ,,
9th ,,	,,	,, ,,	,, ,,
10th ,,	,,	,, ,,	,, ,,

Strong stimulus (ether) first insufflation: significant in series I and II and not significant in series III.

Comment.—In series I, with 50 trials, a significant difference is shown over a wide range. In series III, with only 10 trials, though the index of efficiency remained at nearly 100, the trials are too few to show any possible significant difference because of the high psychological factor in the control group.

Ability to Suppress Vigorous Stimuli

It has been shown that, even in the absence of a cough-suppressant, peppermint water was not a sufficiently strong stimulus to produce 100% cough-response though continued to the 10th insufflation. In the case of ether, however, 95–100% of coughs were produced at the first insufflation, and it is this stimulus which must be used to compare any two drugs. While acknowledging this, it is interesting to note how the efficiency of the drugs is reduced by increasing insufflations of ether (figs. 12–14).

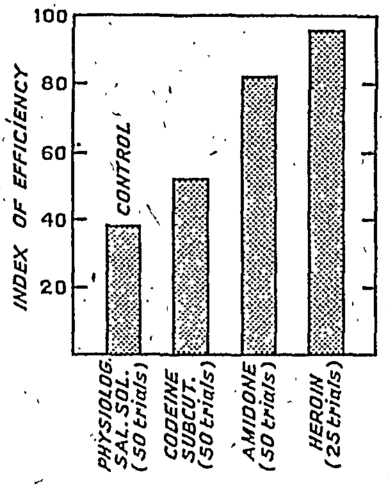


Fig. 10—Efficiency of various drugs in suppressing cough due to 1st insufflation with ether in series II.

The most effective drug in "resisting" the stimulus to coughing provided by ether insufflations was heroin. Morphine shows a sharp decline in series I but its effect is better sustained in series III. This anomaly has already been mentioned and some factor, at present obscure, presumably accounts for it. Amidone is apparently less able than heroin to suppress powerful stimuli.

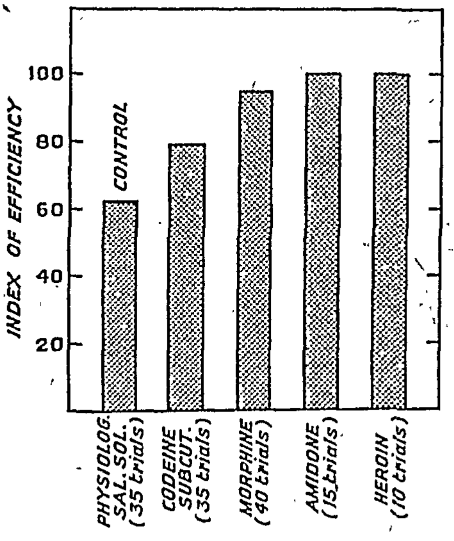


Fig. 11—Efficiency of various drugs in suppressing cough due to 1st insufflation with ether in series III.

RELATION OF COUGH-SUPPRESSING ACTION TO HYPNOTIC EFFECT

All the drugs used have some hypnotic action. As it seemed possible that this alone might explain their cough-suppressant effect, a hypnotic drug was given which is not generally believed to have any specific effect on coughing, so as to test this possibility. In this volunteer pentobarbitone ('Nembutal') gr. $1^1/_2$ was sufficient to cause marked drowsiness.

On five occasions pentobarbitone was administered by capsule, and on a further five occasions an empty capsule was given instead *in random order*. The capsules were placed on the back of the tongue and swallowed immediately while the man kept his eyes tightly closed. The usual trials of peppermint water and ether were made, and the efficiency of the drug to reduce cough expressed.

No significant reduction of coughs was shown in this limited series.

In 81 of the 102 experiments the volunteer was a to express an opinion on the degree of drow produced. The results are shown in table VII.

This is solely an impression gained by the volunte regarding hypnotic effect of the drugs, but it sugges that heroin had the most powerful hypnotic actio Here again the psychological factor is apparent: i 18 of 23 occasions when physiological saline solution w injected, some degree of drowsiness was produced, thoug to a less extent than with potent drugs.

DISCUSSION

The assessment of remedies which give only symp tomatic relief is notoriously difficult. At first sight i might seem a simple matter to decide, by experimenta methods, whether a drug is a valuable cough-suppressan Thus a number of patients with persistent cough migh be asked to give their opinion on the value of the dru under investigation. Experience shows, however, th variation in the threshold for cough-provoking stimu the susceptibility of patients to suggestion, and th tendency to spontaneous improvement are a few of th factors which would make the result of such stud difficult to interpret.

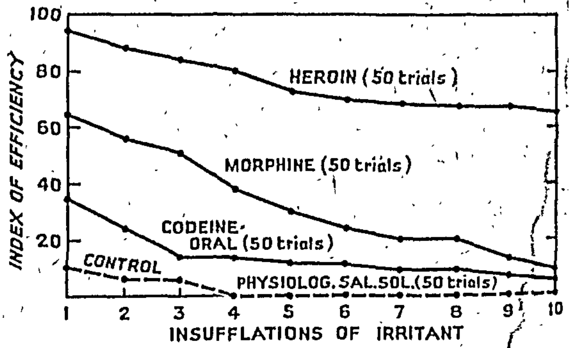


Fig. 12—Efficiency of various drugs in suppressing cough due to ether i series I.

The method described here has several advantages the cough was indistinguishable from that which occur naturally, for the same physiological mechanism wa brought into play; the tests were made on one perso in the course of a year, thus eliminating the experimenta difficulty of allowing for variation from one person t another; and a sufficiently large number of data wer obtained under standard conditions to show that, eve in the most favourable circumstances, results are no easy to predict. It would undoubtedly be interesting t repeat the whole investigation on several other volunteers but there is considerable difficulty in finding volunteer who are as tolerant and coöperative as the man wh submitted to these tests.

An unexpected finding was the great importance o the psychological factor. It lends support to the view that

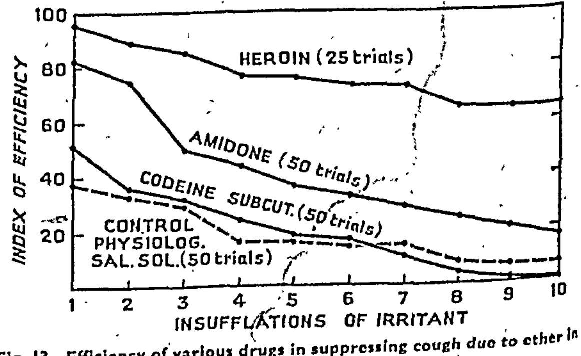
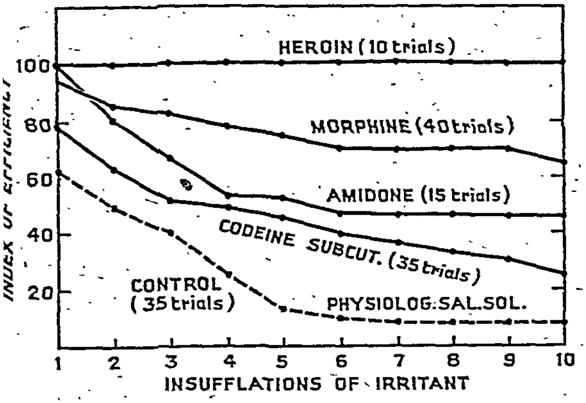


Fig. 13—Efficiency of various drugs in suppressing cough due to ether in series II.



g. 14—Efficiency of various drugs in suppressing cough due to ether in series III.

he placebo has considerable importance in therapeutics. here is the further possibility that the attitude of the octor prescribing a drug may materially affect the esults obtained from the treatment, but it must be mphasised that in the experiments described here the bject of the investigator was to give no indication to he patient about the potency of the preparations dministered.

It might be expected that some degree of habituation o the drugs would arise, or that the patient might ecome increasingly tolerant to laryngeal stimulation. his seems unlikely, because the cough-suppressant ffect did not decrease in the second and third series of xperiments; and there was a tendency for the cough o be provoked by weaker stimuli before treatment as he tests proceeded over a period of months—a finding which contributed to the observed increase in the psycho-cal factor by exaggerating whatever suppressant effect was obtained.

ABLE VI—COMPARISON OF PEPPERMINT WATER AND CONTROL UP TO AND INCLUDING 3RD INSUFFLATION

Injection	No. of coughs		
	Before injection	After injection	Total
Morphine	20	7	27
Control (saline) ..	16	6	22
Total	36	13	49

χ^2 test shows no significant difference in this example.

High doses of the cough-suppressants were deliberately used because it seemed likely that they would be necessary in view of the kind of stimulus used. These quantities —codeine phosphate gr. 1, morphine hydrochloride gr. $^1/_4$, and amidone 15 mg.—were considered to be comparable doses. The dose of diamorphine hydrochloride (heroin) selected was gr. $^1/_6$, erring on the high side.

In clinical practice codeine is widely used to suppress coughing. When given in full doses it is thought to be almost as effective as morphine, and to have the added advantage of being much less likely to cause nausea and constipation.

In this series of experiments no significant degree of cough-suppression could be demonstrated from the administration of codeine phosphate. There are a-priori grounds for supposing that codeine in adequate doses should have an action comparable to that of morphine, but it can only be stated that these experiments have not shown such an effect on coughing. Judged by the results described above, codeine is certainly the least efficient of the drugs examined. On the other hand, morphine has a significant effect, especially on forceful coughing. In the dose of gr. $^1/_6$ heroin was the most efficient cough-suppressant for both weak and strong stimuli.

Admittedly it would be unwise to use heroin for chronic cough, because of the risk of producing addiction. The results of this investigation, however, provide some justification for using heroin as a cough-suppressant for short periods in selected cases, especially where a troublesome cough has not responded to other opiates.

Amidone is a comparatively new drug which has been widely accepted as an analgesic. It shares the disadvantages of the morphine group in tending to depress respiration and to cause nausea; and it is also included among the drugs liable to cause addiction. Nevertheless, judged by the experimental method, amidone is a valuable cough-suppressant.

TABLE VII—HYPNOTIC EFFECTS OF COUGH-SUPPRESSANTS

Suppressant	No. of experiments	Drowsiness			
		None	Slight	Moderate	Severe
Control (saline)	23	21·7%	47·8%	26·0%	4·4%
Codeine inject.	16	12·5%	43·7%	25·0%	18·7%
Morphine ..	14	Nil	21·4%	57·1%	21·4%
Heroin.. ..	15	Nil	13·3%	20·0%	66·6%
Amidone ..	13	Nil	30·8%	53·8%	15·3%

There is no evidence that the cough-suppressant action of a drug is related to its potency as a hypnotic.

SUMMARY

A method is described of provoking the cough reflex by spraying the larynx with irritant solutions of known strengths.

The efficiency of drugs in common use as cough-suppressants was determined, and control observations were made throughout the investigation by using the identical methods after administration of an inert substance (*physiological saline solution*). The experiments are tabulated in three series of trials carried out on 102 occasions; and the findings have been analysed statistically.

It is concluded that morphine, diamorphine, and amidone are potent cough-suppressants, and their relative merits are discussed.

No evidence was obtained in these experiments that the action of codeine is any greater than can be explained by the factor of suggestion.

This psychological factor was apparent in all the experiments, and was sometimes of great importance in contributing to the success of drug treatment.

I am indebted to Prof. Stanley Alstead for his interest in this work. The investigation was initially started in association with Dr. J. C. C. Kelly, and I thank him for his valuable help. Dr. Richard A. Robb, of the mathematics department in the University of Glasgow, kindly planned and undertook the statistical examination of the results.

"... The mental environment of a child has altered greatly during the past century. . . . The baby used to be breast-fed when it cried and remained at the breast as long as it wished; now he is fed by the clock at fixed intervals with total disregard of his natural desires. His training in habits of hygiene is implanted at any early age, and as soon as possible he is inculcated with a sense of shame if he soils his clothes or the floor. The family is small and he has little opportunity for the comradeship with his brothers and sisters which was so excellent a factor in the emotional growth of his ancestors. In the olden days, he drifted into school at any convenient age; at the present time he is jerked into school at the age of five, from the shelter of a family where in most cases, he is king and his wish is law, to what seems to him a brutal environment in which at the best, no one takes any notice of him, or at the worst, he is bullied. He has less friendliness and more discipline than his grandparents, and is subject to much more anxiety."—HUGH PAUL, M.D., *The Control of Communicable Diseases*, London, 1952.

ACUTE MONILIASIS OF THE URINARY TRACT

HERMON TAYLOR
M.D., M.Chir. Camb., F.R.C.S.
SURGEON, THE LONDON HOSPITAL, AND KING GEORGE HOSPITAL, ILFORD

J. A. RUNDLE
M.R.C.S.
HOUSE-SURGEON, KING GEORGE HOSPITAL, ILFORD

THERE is a growing suspicion that the use of antibiotics, while destroying pathogenic organisms, may promote the production of disease by organisms commonly saprophytic (Woods et al. 1951). Infection by *Candida (monilia) albicans* may well be induced in this way, and the present case is reported as a possible example.

Moniliasis of the lungs has been reported occasionally in the last twenty years, and extension to the meninges, presumably by the blood-stream, has been mentioned in four reports (Smith and Sano 1933, Miale 1943, Halpert and Wilkins 1946, Zimmerman, Frutchey and Gibbes 1947). The present case is one of infection of the urinary tract, and we have only been able to find two other cases published. Wessler and Brown (1945) reported a case of monilial cystitis associated with severe febrile illness. Jonxis (1947) published the case of a girl of 7 months with severe enterocolitis, profuse growth of candida from the fæces, and moniliasis of the bladder and kidneys. Blood-cultures were negative, and Jonxis considered that the infection was an ascending one from the vulva.

CASE-RECORD

A woman, aged 56, enormously fat (18 st.), had been well until 5 weeks before admission to hospital. She then complained of generalised headaches and vague abdominal pain. 7 days before admission she developed a cough with sputum, and was treated by her doctor with sulphonamides. Her general condition did not improve, and she was admitted to hospital with a mild hæmoptysis. At this time micturition was normal.

On admission she was clearly very ill, and had a high temperature and a rigor. There was a widespread urticarial rash, and œdema of the ankles. Her blood-pressure was 115/70 mm. Hg, and respirations were 28 per min. She had some tenderness in the upper abdomen.

Treatment and Progress.—She was put on a course of chloramphenicol 2·5 g. daily for 7 days, with considerable improvement in her general condition. However, 2 days later her urine was almost completely suppressed, only 3 oz. being passed on the 3rd day and 1 oz. on the 4th. The urine contained an excess of white cells, some red cells, granulo-hyaline casts, and renal epithelium with a considerable amount of debris. Culture produced a profuse growth of *C. albicans* but no ordinarily pathogenic organisms. At this stage the fungus was thought to be a contaminant, but the oliguria was very puzzling; it was clearly not due to sulphonamides, because there were no crystals in the urine.

Cystoscopy on the 8th day showed diffuse engorgement of both ureteric orifices. Both ureters were catheterised with ease, but only a few drops of urine were obtained. Culture grew *C. albicans* from both ureteric and bladder specimens.

For 10 days the output of urine remained minimal, being 1–11 oz. a day. The blood-urea level was 300 mg. per 100 ml., and the patient had become comatose. Suddenly, however, on the 11th day she passed 42 oz. of urine, and next day 66 oz. Unfortunately this remission was but temporary, and the anuria recurred on the 13th and subsequent days. Nephrostomy was rejected because of the patient's gross obesity and œdema (which now involved the loins), the lack of any demonstrable obstruction to the ureters, and the sudden release of large quantities of urine on the 12th and 13th days.

Repeat cystoscopy on the 15th day showed gross cystitis with much debris in the bladder. The left ureteric orifice was obscured by inflammation of the mucosa. The right side was catheterised again without producing more than a few drops of urine.

Shortly after this the patient again became comato and died on the 17th day after admission.

Necropsy Findings.—Bilateral basal consolidation of th lungs was present to a degree that might be expecte in one who had had such a serious illness for 20 day There was no gross collection of purulent material i the bronchi; nor was any local lesion found in the lung Unfortunately, no culture was made from the lungs. Th myocardium was soft. No abnormality was found in th intestine or in the abdominal viscera. Both kidneys wer enlarged and congested. The capsule stripped easily an showed multiple yellow areas about 1 or 2 mm. in diamete On section these proved to be small abscesses. Both ren pelves and both ureters were distended with yellowish-gre purulent material, which on microscopy proved to contai the mycelium of candida. The mucosa of the pelves an ureters was red and œdematous. There was no anatomic obstruction at any point in the entire urinary tract. Th bladder showed gross cystitis, with petechial hæmorrhage in the submucosa. The contents of the renal pelves wer taken for culture with great precaution to avoid contamination. Dr. J. Spencer reported the presence of pathogeni candida; and Dr. J. Walker, of the London School o Hygiene and Tropical Medicine, identified *Candida albican* and *C. krusei*. Only the former was considered pathogenic.

DISCUSSION

This case is clearly one of urinary moniliasis. Th cause of death seems to have been uræmia, due partl to pyelonephritis and partly to blockage of the ureter with mycelium. Such blockage is suggested by th passage of large quantities of urine on two consecutiv days in the middle of an otherwise progressive and fata anuria. We know of no other condition in which anuri is temporarily interrupted in this way, and the observation may be a significant diagnostic sign. The urinar moniliasis in this case seems to have arisen as a complication of an acute generalised febrile illness which did no respond to sulphonamides but improved at once whe treated with chloramphenicol. It was during thi therapy that the urirary symptoms arose. There wa no macroscopic evidence of moniliasis in any other par of the body.

Probably the fungus entered through the lungs, but the evidence on this point is incomplete.

REFERENCES

Halpert, B., Wilkins, H. (1946) *J. Amer. med. Ass.* 130, 932.
Jonxis, J. H. P. (1947) *Maandschr. Kindergeneesk.* 15, 225.
Miale, J. B. (1943) *Arch. Path.* 35, 427.
Smith, L. W., Sano, M. E. (1933) *J. infect. Dis.* 53, 187.
Wessler, S., Brown, H. R. (1945) *Ann. intern. Med.* 22, 886.
Woods, J. W., Manning, I. H. jun., Patterson, C. N. (1951) *J. Amer. med. Ass.* 145, 207.
Zimmerman, S. L., Frutchey, L., Gibbes, J. H. (1947) *Ibid*, 135, 145.

MONILIASIS PNEUMONIA FOLLOWING AUREOMYCIN THERAPY

F. W. WOLFF
M.B. Durh.
SQUADRON-LEADER, R.A.F.; OFFICER IN CHARGE OF MEDICAL DEPARTMENT OF A R.A.F. HOSPITAL

TREATMENT with antibiotics, especially chloramphenicol, aureomycin, and terramycin, is sometimes followed by moniliasis (Council on Pharmacy and Chemistry 1951); a fatal case of pulmonary moniliasis following treatment of maxillary sinusitis with penicillin, streptomycin, and aureomycin was reported by Ormerod and Friedmann (1951). *Candida albicans*, the causal organism of moniliasis, is a common saprophyte in man; but Davis and Warren (1937) showed that it could become pathogenic and cause fatal pulmonary moniliasis, even without the action of antibiotics.

The bacteriostatic action of the antibiotics seems to upset the natural balance of the flora of the body and to enable those exempt from it to flourish excessively and even to change from saprophytes to pathogens.

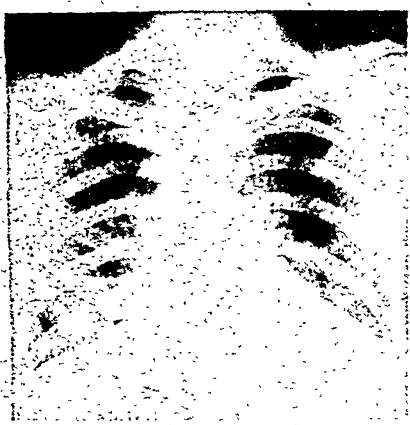


Fig. 1—Bilateral basal lung lesions, with a little fluid on the left side.

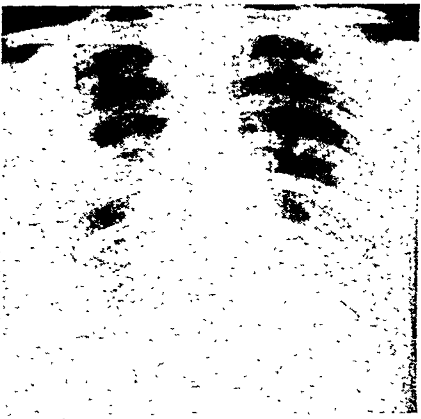


Fig. 2—Extension of disease to right upper lobe.

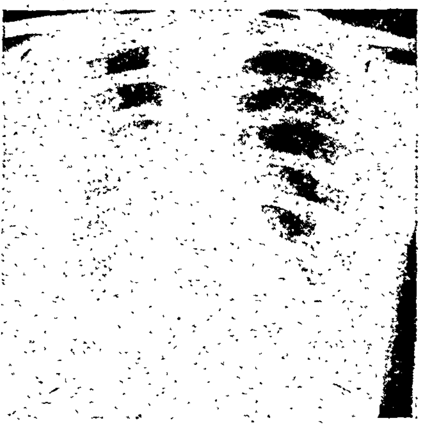


Fig. 3—Condition deteriorating.

In the case reported here the clinical picture deteriorated steadily under antibiotic therapy, with relevant changes in the bacteriology of the sputum, and the cessation of such treatment was followed by rapid and continuing improvement.

CASE-RECORD

The patient was a stoker mechanic in the Royal Navy, aged 22. Ten days after arriving on home leave from the Far East, he developed a cold with cough and blood-streaked sputum.

On admission to hospital on Dec. 7, 1951, he was only moderately ill. Examination of his chest suggested bilateral basal lung lesions, with a little fluid on the left side. Aspiration produced a little straw-coloured fluid. Radiography (fig. 1) confirmed the diagnosis. The sputum before treatment showed a fair growth of *Hæmophilus influenzæ* and *Neisseria catarrhalis*, which were sensitive to aureomycin, chloramphenicol, and streptomycin, feebly sensitive to sulphonamides, and insensitive to penicillin. A white-cell count showed 16,000 per c.mm. (polymorphs 82%).

Treatment and Progress.—Before the report on the sputum was obtained, treatment was started with penicillin and sulphonamides in full doses. Three days later the patient seemed much better and his temperature had almost subsided. On Dec. 17, he complained of severe pain in his right chest, and his temperature went up to 103°F. His sputum became very bloodstained, and radiography (fig. 2) showed that the disease had extended to the upper lobe. The sputum at this stage contained mostly *H. influenzæ* and pneumococci sensitive to streptomycin and aureomycin. By Dec. 20 he was extremely ill, with severe pleuritic pain, frequent hæmoptysis, and dyspnœa. The white-cell count had risen to 24,400 per c.mm. (polymorphs 83%). The radiographical appearances are shown in fig. 3. Aureomycin 500 mg. six-hourly and streptomycin 0·5 g. twice a day were given. During seven days of this treatment he deteriorated rapidly; he was sweating profusely and had pyrexia and a cough with much bloodstained sputum, which on Dec. 23 was swarming with large clumps of yeast-like organisms resembling candida. No tubercle bacilli were found; but culture produced almost a pure growth of organisms morphologically resembling *Candida albicans*.

By Dec. 27 the patient was apparently moribund. Radiologically large cavities had appeared in the right upper lobe with fluid levels (fig. 4). He was too weak to coöperate in postural drainage and had temporary retention of urine. A white-cell count on Dec. 28 showed 30,000 per c.mm., and his temperature remained at 104°F. Repeated examinations of his sputum showed complete absence of ordinary pyogenic organisms, their place being taken by fungi and yeast. All treatment with antibiotics was suspended by Dec. 29, and all attention was directed to obtaining an adequate intake of fluids, glucose, first-class proteins, and alcoholic stimulants in small doses. By Jan. 3, 1952, a remarkable change had taken place in his condition: his temperature was falling by lysis; he felt better, and was overcoming his severe depression; his sputum became purulent; and he coöperated in postural drainage. Radiography on Jan. 5 showed some resolution of the consolidation surrounding the cavities (fig. 5). A white-cell count on this day showed 18,000 per c.mm. (polymorphs 80%). The sputum contained numerous gram-positive cocci, and culture produced an almost pure growth of coagulase-positive staphylococci sensitive only to streptomycin and penicillin.

Even though much improved the patient still had an evening temperature up to 101°F and sweated profusely. For fourteen days he was given penicillin 1,000,000 units six-hourly and streptomycin 0·5 g. b.d. Progress after this was uninterrupted. Radiography on Jan. 21 showed much improvement and

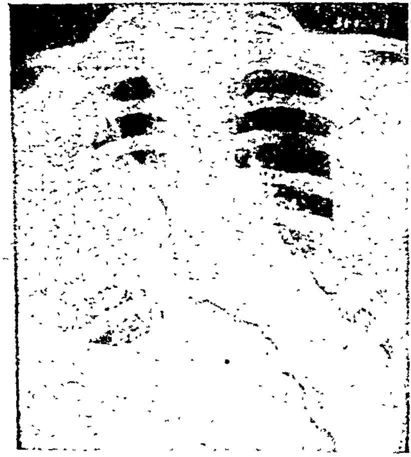


Fig. 4—Large cavities in right upper lobe.

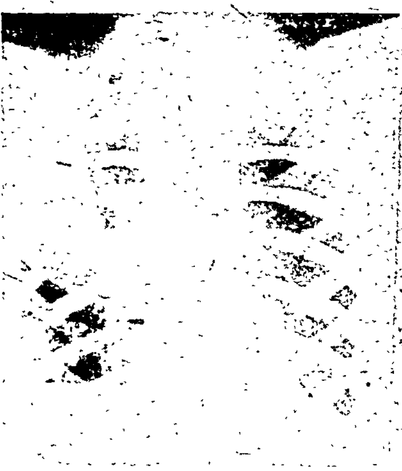


Fig. 5—Resolution of consolidation surrounding cavities.

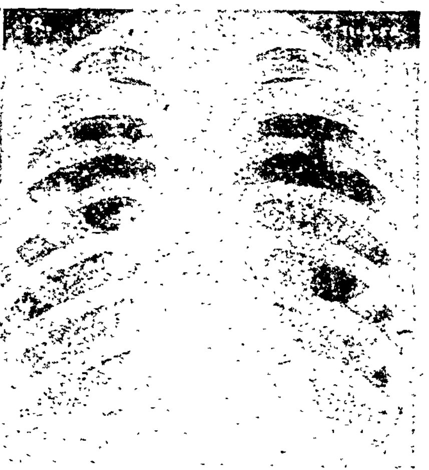


Fig. 6—Only a small contracted scar remains in right lung.

contraction of the cavities. On Jan. 31 radiography showed only a small contracted scar in the right upper lobe (fig. 6), and there was no sputum. On Feb. 3 the patient developed infective hepatitis after a short prodromal period of malaise and anorexia. This did little to hold up his recovery. On March 1 he was very well and had no cough.

SUMMARY

A case is described in which the treatment of pneumonia with aureomycin and streptomycin, to which the organisms in the sputum had been shown to be sensitive, led to a change of the bacterial flora responsible for the infection, *H. influenzæ* and *N. catarrhalis* being superseded by *Candida albicans*, and very serious clinical deterioration. Cessation of treatment with antibiotics was followed by recovery.

In treating chest infections with antibiotics, especially aureomycin, such undesirable effects might be avoided by giving the antibiotic in short courses alternating with periods of rest to re-establish the normal balance of the flora of the upper respiratory tract.

Thanks are due to the sisters and nursing orderlies of this R.A.F. hospital, whose devoted care was mainly responsible for this patient's recovery, and to the Director-General of the Royal Air Force Medical Service for permission to publish.

REFERENCES

Council on Pharmacy and Chemistry (1951) *J. Amer. med. Ass.* **145**, 1267.
Davis, A. H., Warren, E. L. (1937) *J. Lab. clin. Med.* 22, 687.
Ormerod, F. C., Friedmann, I. (1951) *Brit. med. J.* ii, 1439.

RESUSPENSION IN PLASMA OF HUMAN RED BLOOD-CELLS FROZEN IN GLYCEROL

J. E. LOVELOCK
Ph.D. Lond.

From the National Institute for Medical Research, Mill Hill, London

THE use of glycerol to prevent hæmolysis during freezing and thawing has been reported by Smith (1950) and Sloviter (1951a and b). They found that red blood-cells could be frozen to −79°C, and later thawed with very little hæmolysis, if suspended in a medium containing 10–20% of glycerol. Red blood-cells which have been suspended in such a medium, whether frozen or not, hæmolyse rapidly when transferred to a medium isotonic with their plasma, presumably because the glycerol within the cells increases their internal osmotic pressure sufficiently for disruptive lysis to take place. Therefore the glycerol must be removed before the thawed cells can be used.

A method of slowly removing glycerol from red blood-cells has been described by Sloviter (1951b). It consists essentially in dialysing the glycerol-treated cells against successively weaker solutions of glycerol in saline solution until the concentration within the cells is low enough for them to be mixed with plasma without the occurrence of hæmolysis.

The removal of glycerol from red blood-cells by dialysis is entirely satisfactory in avoiding hæmolysis but is slow and may be difficult to manage under practical conditions. This note describes an alternative method of reconstitution in which the glycerol is removed from the thawed red blood-cells by increasing the osmotic pressure of the suspending medium by the addition of some substance to which the cells are relatively impermeable. The glycerol-free cells may then be separated by centrifuging and resuspended, if desired, directly in plasma.

METHOD

Human red blood-cells which have been frozen and thawed in a medium containing 15% glycerol are subjected to the increased external osmotic pressure obtained by adding to the thawed suspension sufficient sodium citrate to raise the concentration to 0·33 *M*, or sufficient glucose to give a concentration of 1·0 *M*. After the addition of the sodium citrate or the glucose the cells are left for five minutes at a temperature not less than 20°C to allow the glycerol to escape from the cells. At temperatures below 20°C the rate of escape of residual glycerol may not be sufficiently rapid to avoid some hæmolysis. The cells are then separated by centrifugation and may be resuspended directly in saline solution or in plasma. It is preferable to use saline solution or plasma at 37°C for resuspension. The pH of the suspension should not be allowed to fall below 7·0 during these operations; at low pH values the ability of the red cell to withstand osmotic shock is weakened. Further, it is most important that contamination with copper or other heavy metals should be avoided, because the transport of glycerol across the red-cell membrane is greatly decreased by traces of these elements (Jacobs 1950).

PRACTICAL APPLICATION

The following example illustrates the practical application of this method:

100 ml. of packed human red blood-cells was suspended in 200 ml. of a solution composed of NaCl 0·135 *M*, NaH_2PO_4 *0·005 M*, Na_2HPO_4 *0·005 M*, *glucose 0·02 M*, and *glycerol* 2·0 *M*, and left for ten minutes at room-temperature to allow the attainment of an equilibrium concentration of glycerol within the cells (Sloviter 1951b).

The suspension was then frozen by immersing in a bath at −79°C and left at this temperature for twenty-four hours. The suspension was next thawed by immersing in a water-bath at 40°C, and removed when the temperature reached 22°C. 150 ml. of 1·0 *M* sodium citrate was added to the 300 ml. of thawed cells, and the mixture was left for five minutes and then centrifuged. *The cells were resuspended in* 10 volumes (1 litre) of buffered saline solution pH 7·0 at 37°C and left for ten minutes, after which they were washed thrice more, each time by centrifuging and resuspending in a further 10 volumes of saline solution.

In practice the repeated washing is not necessary. It was included here to illustrate that the absence of hæmolysis on first suspending the cells in saline solution was not due to a carry-over of citrate and glycerol with the cells. The extent of hæmolysis during each stage of the operations just described was as follows:

Operation	*Hæmolysis %*
Freezing and thawing	8·2
Addition of sodium citrate to thawed suspension	0·2
Resuspension in buffered saline	2·1
1st washing with saline	0·2
2nd washing with saline	0·2
3rd washing with saline	0·2

The cells recovered by this process are normal in appearance and have the same resistance to hypotonic media as have the original cells.

PRINCIPLE

The operation of the process just described may be briefly explained as follows. Red blood-cells which have been suspended for some time in a medium containing 2·0 *M* glycerol contain this concentration of glycerol within them and therefore are not subjected to any excess external osmotic pressure. It follows that the addition of 1·0 *M* glucose or 0·33 *M* sodium citrate to the medium produces an approximately sevenfold increase in the external osmotic pressure (assuming the salt concentration within the red blood-cells to be 0·16 *M*). Glycerol and water will then leave the cells until the internal salt concentration has risen so as to establish osmotic equilibrium. When equilibrium is reached the cells will contain only a seventh of the quantity of glycerol and water that they originally possessed, and can therefore be safely transferred to saline solution or to plasma without the production of an excessive internal osmotic pressure.

SUMMARY

A method is described for the rapid removal of glycerol rom red blood-cells which have been frozen and thawed n media containing glycerol.

Red blood-cells so treated may be directly resuspended n saline solution or in plasma without the occurrence f hæmolysis.

I am indebted to Dr. H. A. Sloviter for his interest and dvice.

REFERENCES

Iacobs, M. H. (1950) *Ann. N.Y. Acad. Sci.* 50, 824.
loviter, H. A. (1951a) *Lancet*, i, 823.
— (1951b) *Ibid*, p. 1350.
mith, A. U. (1950) *Ibid*, ii, 910.

INSULIN HYPOGLYCÆMIA AND THE EOSINOPHIL-COUNT

F. MACKENZIE SHATTOCK
M.A. Oxfd, M.D. Lond., D.P.M.
CONSULTANT PSYCHIATRIST

LORNA P. MICKLEM
B.Sc. Lond.
RESEARCH ASSISTANT

CLINICAL RESEARCH UNIT, THREE COUNTIES HOSPITAL, ARLESEY, BEDS.

THE observation by Hills et al. (1948) that stimulation of the adrenal cortex is followed by a reduction in the number of circulating eosinophils has led to the adoption of "induced eosinopenia" as a test of cortical activation. This reaction can be initiated by the injection of A.C.T.H., by hypoglycæmia, burns, trauma, surgical operation, or electroconvulsive therapy (E.C.T.), or by exposure to cold and other stresses, as well as by the injection of oxycorticosteroids. The maximal fall in the eosinophil-count occurs three to four hours after the administration of A.C.T.H. and six to seven hours after the injection of insulin in adequate dosage. Criticism of the test is based mainly—and justifiably—on the occurrence of occasional positive responses in patients with Addison's disease, and the issue has been confused by the use of adrenaline as an adrenocortical stimulus. Recant et al. (1950) are inclined to attribute anomalous responses to the survival of remnants of functional adrenal tissue, but Thorn (1950) has stated that "epinephrine eosinopenia" may occur after complete bilateral adrenalectomy for hyperpiesis. He is certain, however, that eosinopenia following A.C.T.H. is "a highly reliable indication of cortical activation of 11, 17-oxysteroids." Sayers (1950) is of the same opinion. He regards an eosinopenic reaction to stress as "the best available test of adrenocortical responsiveness, in man."

It is now generally recognised that large doses of adrenaline may provoke an early eosinopenia, which is well-marked one hour after injection (Long 1950), and that this reaction may be followed by a prolonged and major depression of the count two to three hours later, when oxycorticosteroids are liberated by the action of A.C.T.H.

SPONTANEOUS VARIATIONS IN EOSINOPHIL-COUNT

Thorn et al. (1948) have suggested that a reduction of more than 50% in the eosinophil-count, occurring three to four hours after the injection of 25 mg. of A.C.T.H., should be regarded as a positive reaction. Most observers accept Thorn's test as the measure of cortical activation, but Rud (1947) has pointed out that "spontaneous" variations of the same magnitude also occur. He has observed day-to-day variation in the same patient, and a fairly constant daily rhythm showing characteristic early morning decreases in the count, with a minimum between 9 and 11 A.M., followed by a continuous rise. In attempting to interpret the significance of induced eosinopenia, Swanson et al. (1952) have suggested that the morning is an unsuitable time for measuring induced reactions in the count, because spontaneous changes may then be as great as 50%, whereas in the afternoon these are less than 40%.

We have confirmed Rud's observation that the eosinophil-count tends to rise in the afternoon and have found that a comparison of 10 A.M. and 2 P.M. counts will avoid the confusing midday irregularities which he noted.

The 2 P.M. count in 40 patients taken on fifty days on which no physical treatment was given, showed only minor changes from the 10 A.M. count. Usually there was a rise, occasionally a fall of less than 50%; and in 2 patients, for no apparent reason, this fall was greater than 50%. In contrast a fall of this magnitude was recorded with striking regularity three to four hours after the onset of hypoglycæmic coma (seven hours after injection of adequate doses of insulin) in 27 patients observed on sixty-seven separate occasions. The same decrease in the eosinophil-count was observed four hours after E.C.T., on approximately two-thirds of forty-nine occasions on which this treatment was given to 37 patients (Shattock and Micklem 1952). Each eosinophil-count was made by the technique of Randolph (1949), and involved 8 separate counts from two pipettes. Results which did not conform to the expected degree of reliability were discarded.

A major spontaneous variation was exceptional in the afternoon counts of our patients (the counts were taken two-hourly on days when no physical treatment was given). This is, we believe, related to the experimental conditions, which included rest in bed and avoidance of physical and mental stresses other than those which were deliberately introduced. It is apparent from work recently published that considerable care has been taken to eliminate technical errors in counting, but that less attention has been paid to the conditions under which these clinical tests are made; both controls and patients sometimes follow their normal occupations—e.g., medical and nursing duties and, for patients, physiotherapy. If eosinopenia is evidence of adrenocortical response to physical and mental stress, these occupations must provide opportunities for so-called "spontaneous" depressions of the eosinophil-count.

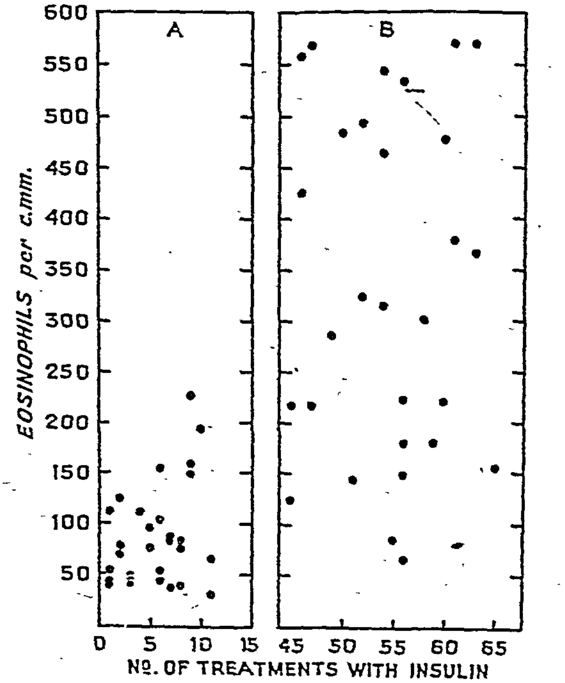


Fig. 1—Individual resting level of eosinophil-counts of patients after (A) 0-15 and (B) 45-65 treatments with insulin.

RISING EOSINOPHIL-COUNT

A gradual rise in the resting level of the eosinophil-count during treatment with insulin or leptazol (' Cardiazol '), or during E.C.T. has been reported by Rud (1947) and Sackler et al. (1951). We have observed this rise, which was usually evident before the eighth hypoglycæmic treatment. The mean value of the morning count in patients who had received between forty-five and sixty-five treatments was significantly higher than that of patients who had received up to twelve treatments only. The mean count of 29 patients after forty-five to sixty-five treatments was 345 eosinophils per c.mm. (standard deviation 189 and range 67–826). The mean count of 30 patients who had received up to twelve treatments was 85 eosinophils per c.mm. (standard deviation 49 and range 30–227). The probability that this difference is a chance occurrence is less than 1 in 10^{10} (fig. 1).

During the early weeks of daily treatment with insulin the eosinophil-count may rise steeply. In 9 cases insulin dosage was rapidly increased to between 120 and 500 units during the second week, and the eosinophil-count rose soon after the fifth treatment. In 2 patients whose insulin was increased more gradually to 60 units in the second week, there was no rise in the eosinophil-count (fig. 2).

Rud (1947) and Sackler et al. (1951) considered that the rising eosinophil-count was of therapeutic importance and that it indicated a patient who may benefit from physical treatment. We were unable to confirm their conclusion; a rise in the number of eosinophil cells was found both in patients who recovered and in those whose clinical progress was disappointing. Whatever its significance it is remarkable that the eosinophil-count should rise at a time when physical treatment is daily reducing the number of eosinophils in the capillary blood. Less than twenty hours after a maximal depression of the count the loss is more than made good (fig. 3). The physiological mechanism which controls this reaction is unknown and it is therefore impossible to say whether the rise in the resting level is caused by overproduction following destruction, or by cumulative re-entry of cells temporarily " blocked " in the bone-marrow or stored in the tissues. Quittner et al. (1951) observed temporary blocking of granulocytes in the marrow of the mouse when the peripheral count was low, but no increase in the proportion of eosinophils followed a massive dose of cortisone.

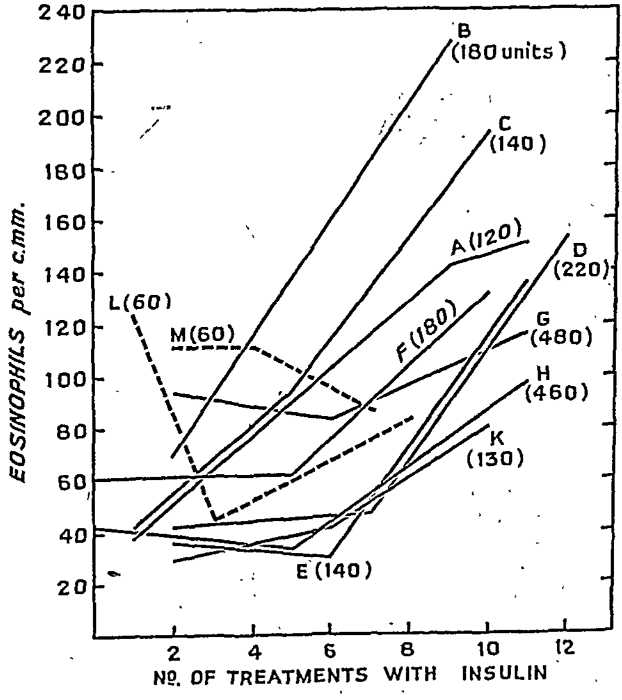


Fig. 2—Rise in resting eosinophil-counts of 9 patients on rapidly increasing doses of insulin (A–K) and 2 on low doses (L and M). Figures on graph give maximum daily dosage of insulin.

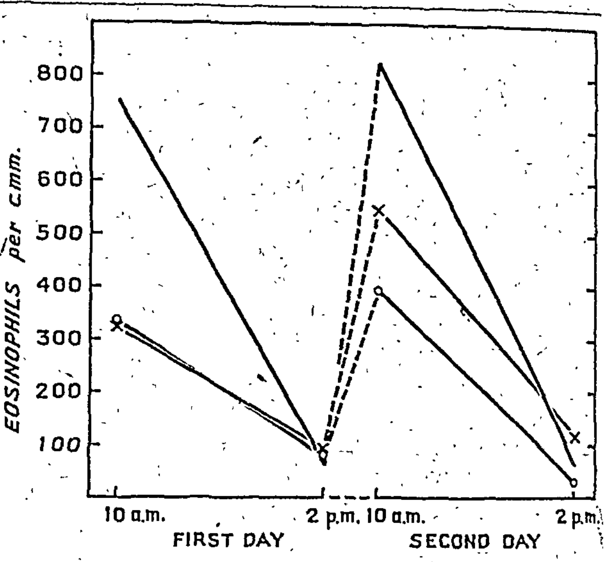


Fig. 3—Eosinopenic reactions of 3 patients. Insulin given at 7 a.m.; onset of coma at 10 a.m.

REPLACEMENT OF EOSINOPHILS

Experimental evidence suggests that when lymphocytes are reduced by cortical stimulation they may re-enter the bone-marrow (Yoffey et al. 1951), but there is no similar evidence to show that mature eosinophils return to the marrow when their number is diminished in the peripheral blood. Spain and Thalhimer (1951) have reported splenic eosinophilia in mice after cortisone injection. If their isolated observation is confirmed it may throw light on the disposal of eosinophil cells.

The neutrophilia which follows repeated hypoglycæmia suggests greater activity of the bone-marrow. Rud has noted such neutrophilia after insulin hypoglycæmia and E.C.T., Hills et al. (1948) and Forsham et al. (1948) after A.C.T.H., and Perera et al. (1949) after 11-dehydro-17-hydroxycorticosterone. We have confirmed a rise in the total white-cell count of the majority of our patients undergoing insulin-coma treatment. The white-cell count rose to between 10,000 and 20,000 cells per c.mm. and the differential count showed that this rise was due to an increase in neutrophil cells. Neutrophilia is not necessarily a consequence of cortical stimulation: A.C.T.H. (Hills et al. 1948, Palmer et al. 1951) and adrenaline (Stein et al. 1951) have been found to have a direct stimulating action on the bone-marrow; under some circumstances this action is also observed in adrenalectomised animals. We cannot say whether the change in the white-cell count of our patients should be attributed to secretion of adrenaline, to A.C.T.H., or to cortical stimulation, but it suggests increased activity of the bone-marrow.

A left shift was observed in the peripheral neutrophil-count in 17 of the 22 patients whose neutrophils were counted (by Cooke's technique) after repeated hypoglycæmia. In each case 100 cells were counted. The number of group I and II cells in these 17 patients exceeded the upper limit of normal, which is said by Whitby and Britton (1946) to be 45%, and in 4 patients these cells exceeded 70% of the total count. It seems likely that the unusually high proportion of immature granulocytes in the peripheral blood is the result of greater activity of the bone-marrow provoked by repeated hypoglycæmia.

STERNAL BIOPSY

The bone-marrow of 10 patients, who had received twenty to sixty hypoglycæmic treatments, was obtained by sternal biopsy; 0·25 ml. was aspirated and 300–500 nucleated cells were counted. The bone-marrow picture was normal and the mean eosinophil-count varied between 3% and 9%. The weighted mean of the eosinophil-count of bone-marrow is 3%, and its 95% range is 1 to 5% (Osgood and Seaman 1944). In 3 of our patients the bone-marrow eosinophil-count was slightly higher than the accepted upper limit of the normal range; in 2 others it was just within this limit. Of more importance perhaps is the unusual proportion of immature eosinophils in 8 of our 10 patients. In 1 of them this proportion was as high as three to one. The patient who had the highest eosinophil-count (9%) showed, however, an inverse proportion of immature to mature cells—an excess which suggests over-production or possibly retention of mature eosinophils in the bone-marrow (see table).

EOSINOPHILS IN STERNAL MARROW OF 10 PATIENTS AFTER 20–60 TREATMENTS WITH INSULIN

Patient	Total eosinophils (%)	Immature eosinophils (%)	Mature eosinophils (%)
1	3	2	1
2	8	6	2
3	4	3·3	0·7
4	3	2·2	0·8
5	6	4	2
6	3·5	2	1·5
7	4	2·7	1·3
8	5	3·3	1·7
9	5	3·8	1·2
10	9	3	6

CONCLUSIONS AND SUMMARY

The use of the induced eosinopenia as a measure of adrenal cortical stimulation is complicated by spontaneous variations in the eosinophil-count. Most of these can be avoided by eliminating physical and mental disturbances other than those under investigation.

A comparison of 10 A.M. and 2 P.M. counts is recommended when the event which initiates eosinopenia can be timed to take place at approximately 10 A.M.

When insulin treatment is given for mental illness the majority of patients after the first week show a rise in the resting level of the eosinophil-count. After repeated hypoglycæmic comas the eosinophil-count is likely to be significantly higher than at the start of treatment.

That repeated hypoglycæmia increases the activity of the bone-marrow is suggested by a rise in the resting level of the eosinophil-count, by the occurrence of neutrophilia, by a left shift in the peripheral neutrophil-count, and by a preponderance of immature eosinophil cells in the bone-marrow.

We are indebted to Dr. Neil McDiarmid, medical superintendent of the Three Counties Hospital, for the clinical facilities and the use of hospital records, and to Dr. J. Munro Sherriff for the bone-marrow biopsies.

REFERENCES

Forsham, P. H., Thorn, G. W., Prunty, F. T. G., Hills, A. G. (1948) *J. clin. Endocrinol.* 8, 15.
Hills, A. G., Forsham, P. H., Finch, C. A. (1948) *Blood*, 3, 755.
Long, C. N. H. (1950) *In* Proceedings of 2nd Conference on Adrenal Cortex. New York; p. 72.
Osgood, E. E., Seaman, A. J. (1944) *Physiol. Rev.* 24, 46.
Palmer, J. G., Cartwright, G. E., Wintrobe, M. M. (1951) *In* Proceedings of 2nd Clinical A.C.T.H. Conference. Philadelphia and London; vol. 1, p. 438.
Perera, G. A., Pines, K. L., Hamilton, H. B., Vislocky, K. (1949) *Amer. J. Med.* 7, 56.
Quittner, H., Wald, N., Sussman, L. N., Antopol, W. (1951) *Blood*, 6, 513.
Randolph, T. G. (1949) *J. Lab. clin. Med.* 34, 1696.

References at foot of next column

Reviews of Books

Bone Lesions of Yaws in Uganda

C. J. HACKETT, M.D., F.R.C.P., director, Wellcome Museum of Medical Science, London. Oxford: Blackwell Scientific Publications. 1951. Pp. 194. 45*s.*

THIS is the most detailed study yet made of the bone lesions in yaws; and Dr. Hackett is to be congratulated on having gathered such a wealth of material. The data which he offers the reader demand close study, but the effort is well worth while. He describes fully the natural history of the stages of the disease from the clinical and radiological viewpoint, and compares the bone lesions of yaws with those of syphilis. This comparison shows that we do not yet know enough about syphilitic bone lesions in Africans, and may stimulate closer examination of the subject. The illustrations are many and good.

This book, which has long been needed by doctors in tropical practice, does much to clarify the evolution of the disease process in yaws, and it is an important contribution.

The United States Public Health Service 1798–1950

RALPH CHESTER WILLIAMS, M.D., assistant surgeon-general, U.S. Public Health Service. Washington D.C.: Commissioned Officers Association of the U.S. Public Health Service. 1951. Pp. 890. $7.50.

IN this handsome and well-illustrated volume, Major-General Williams, who holds a distinguished position in the U.S. Public Health Service, gives us its history from its origin in 1798 to 1950.

It was created by an Act of Congress in 1798 requiring the Federal government to provide hospitals for American merchant seamen and to deduct 20 cents per month from each man's wages to build up a fund to finance the hospital scheme, which in the following year was extended to the U.S. Navy. So the U.S. Public Health Service began in applying compulsory health insurance to American seamen. The first hospital erected by the government was the Boston Marine Hospital, which was opened in 1804. In 1807 Harvard medical students were admitted, as students, to the wards, and thus the hospital became the first teaching hospital in the United States. Hospitals for seamen were soon provided in other ports; and under an Act passed in 1929 the service erected two hospitals for persons addicted to narcotic drugs.

The service now operates 24 hospitals, with about 8170 beds, 19 outpatient clinics, and 103 outpatient offices. Since 1925 it has furnished medical advice by radio to ships at sea. Its activities were greatly extended in 1883, when it was charged with the responsibility of protecting the nation from invasion by epidemic disease. At that time yellow fever was a serious menace to the southern States, and strict quarantine regulations were imposed. The development of this work and its extension to airborne traffic, are well described. The millions of immigrants that swarmed into the United States in the early years of this century caused various difficult health problems, in the solution of which the service showed remarkable ingenuity and resource. The rapid advances made during the last fifty years in the prevention and cure of disease have enormously extended the functions not only of the service, as the Federal health authority, but of the State and local county and city authorities. Public-health administration in America presents what at first sight appears to be a series of complicated patterns,

DR. SHATTOCK, MRS. MICKLEM: REFERENCES (*contd*)

Recant, L., Hume, D. M., Forsham, P. H., Thorn, G. W. (1950) *J. clin. Endocrinol* 10, 187.
Rud, F. (1947) *Acta psychiat., Kbh.* suppl. 40, p. 1.
Sackler, R. R., Sackler, M. D., Sackler, A. M., Greenberg, D., Van Ophuijsen, J. H., Tui, C. (1951) *Proc. Soc. exp. Biol., N.Y.* 76, 226.
Sayers, G. (1950) *Physiol. Rev.* 30, 241.
Shattock, F. M., Micklem, L. P. (1952) *J. ment. Sci.* 98, 287.
Spain, D. M., Thalhimer, W. (1951) *Proc. Soc. exp. Biol., N.Y.* 76, 320.
Stein, K. F., Martin, C., Falk, D. (1951) *Ibid*, p. 110.
Swanson, J. N., Bauer, W., Ropes, M. (1952) *Lancet*, i, 129.
Thorn, G. W. (1950) *In* Proceedings of 2nd Conference on Adrenal Cortex. New York; p. 64.
— Forsham, P. H., Prunty, F. T. G., Hills, A. G. (1948) *J. Amer. med. Ass.* 137, 1005.
Whitby, L. E. H., Britton, C. J. C. (1946) Disorders of the Blood. London.
Yoffey, J. M., Metcalf, W. K., Herdan, G., Nairn, V. (1951) *Brit. med. J.* i, 660.

but in practice the complications often turn out to be more apparent than real.

The book is not only informative but unfailingly interesting.

Practical Procedures

2nd ed. Editors: Sir HENEAGE OGILVIE, K.B.E., D.M., M.CH., F.R.C.S.; W. A. R. THOMSON, M.D. London: Eyre & Spottiswoode for the *Practitioner*. 1952. Pp. 380. 25*s*.

THE latest volume of the Practitioner Handbook series is not a newcomer but a much revised version of the original pre-war edition. Its aim is still to allow those who have practised the classical procedures to describe them simply but fully so that the family doctor or hospital resident understands their use and how to carry them out. There is certainly room for a collection of articles of this kind put together by such experienced authors.

The 27 chapters contain just under 100 illustrations and diagrams. Most of the procedures described are surgical, and range from plaster-of-paris techniques, local anæsthesia, and syringing of the ear, to operations such as circumcision and minor surgical affections of the skin—an admirably pungent and informative chapter by Mr. A. Dickson Wright. Other articles describe methods of investigation: the technique and value of blood-counts is covered by Sir Lionel Whitby; and lumbar puncture by Dr. W. G. Wyllie. Of the 10 chapters added since the last edition, some deal with old procedures, such as the examination of the rectum, but others mark the advances of recent years, and include the administration of penicillin and streptomycin, hormone implantation therapy, and the technique of biopsy.

The book will prove a useful friend to the practising doctor, to the young resident, and sometimes perhaps to the too theoretically minded consultant and teacher.

Factors Regulating Blood Pressure

Transactions of the Fifth Conference. BENJAMIN W. ZWEIFACH and EPHRAIM SHORR. New York: Josiah Macy, Jr., Foundation. 1951. Pp. 238. $3.75.

THE Josiah Macy, Jr., Foundation's fifth conference on factors regulating blood-pressure dealt almost exclusively with atherosclerosis and arteriosclerosis, although, as Dr. H. Goldblatt pointed out, neither their rôle as a possible organic basis of hypertension nor their own ætiology and pathogenesis have yet been satisfactorily elucidated. The subjects considered included the blood chemistry in arteriosclerosis, lipoproteins and atherosclerosis, the regulation of fat deposition, experimental hypertension, the incidence of arteriosclerosis in Scandinavia during the war, the changes in the media in arteriosclerosis and hypertension, experimental renal hypertension, and cholesterol atherosclerosis. Often the presentation and discussion reached a high standard, providing stimulating thoughts both for those researching in this field and for physicians dealing with the results of atheroma in the clinic. Of particular merit is the paper by Gofman and the subsequent discussion on lipoproteins and the importance of S_f 10–20 lipoproteins, offering strong support to Katz's conclusion that atherosclerosis is a metabolic disease with hope for ultimate prevention and cure. This volume provides a fascinating insight into the vast amount of brilliant and painstaking work now being carried out by American investigators.

The Life and Work of Astley Cooper

R. C. BROCK, M.S., F.R.C.S., F.A.C.S., surgeon to Guy's Hospital, London. Edinburgh: E. & S. Livingstone. 1952. Pp. 176. 20*s*.

Sir Astley Cooper of Guy's Hospital is remembered as a keen and generous supporter of the body-snatchers, as the man who once dissected an elephant, and as the uncle of the Bransby Cooper whose surgical skill was attacked in our columns. But his real claims to distinction are less well known, and in this entertaining biography Mr. R. C. Brock shows the extent and value of his contributions to surgery.

Astley Cooper used catgut for arterial ligation fifty years before Lister made the method safe. His practical and experimental work on arterial surgery culminated in his ligation of the abdominal aorta in a case of aneurysm. He successfully amputated through the hip-joint in 1824, many years before anæsthetics and antiseptics were known. His brilliant published works show his original mind and experimental approach, and make it hard to understand the critics who saw in him only a worldly gold-loving surgeon of no scientific attainments. In the preface to his greatest book, on *Hernia*, he wrote "I have related no case and given no remark to the truth of which I cannot vouch." That was the standard of his work and of his teaching. Until the publication of this biography, Astley Cooper had not been accorded the honour and esteem due to him.

The Ethical Basis of Medical Practice

WILLARD L. SPERRY, D.D., dean of Harvard Divinity School. London: Cassell. 1951. Pp. 185. 12*s*. 6*d*.

THE recognised code of medical ethics gives the doctor little help in deciding between conflicting loyalties when there is no forthright clash between right and wrong. A Rh-negative patient who has had repeated hæmorrhages is beyond the reach of curative treatment; only blood-transfusions will help, and Rh-negative blood is scarce. Should the doctor use some of the limited supply or save it for others whose lives might be saved? Should a patient with an incurable disease be told that cure is impossible? These are the kind of problems which Professor Sperry discusses.

He points out that only 6 out of 22 pages of the booklet of the American Medical Association on professional medical conduct deal with the doctor's duties to the patient and public, while 16 pages are given to the duties of doctors to each other and their profession. Though lawyers, professors, and theologians attack each other, sometimes mercilessly, doctors stand together to defend the good name of their profession, and Professor Sperry maintains that in the conventional code of ethics the patient's interests are not given first place.

S.F.A. Catalogue of Medical Films (London: Harvey & Blythe. 1952. Pp. 195. 15*s*.).—The catalogue of medical films which the Scientific Film Association published with the Royal Society of Medicine in 1948 is out of print and out of date. To replace it the S.F.A. have produced this fuller edition. The new catalogue contains a classified list of films, a key to distributors and owners, and an index of film titles. The informative summary of the contents of each film which has also been added to this edition will help many harassed selectors.

Recent Advances in Medicine (London: J. & A. Churchill. 1952. Pp. 397. 27*s*. 6*d*.).—The advances of five years have meant new chapters on the collagen diseases, the anti-histamine drugs, and the use of isotopes in medicine. The chapter on antibiotics has been expanded to include aureomycin, chloramphenicol, streptomycin, and terramycin. Sections have also been added on vitamin B_{12}, unipolar leads in electrocardiography, cardiac catheterisation, the methonium salts, the treatment of tuberculosis with streptomycin and *p*-aminosalicylic acid, and much else. A comparison with the 12th edition shows how thorough has been the revision, and how closely the authors, Dr. G. E. Beaumont and Prof. E. C. Dodds, follow upon the heels of progress in a race they have now been running for 28 years.

Modern Treatment Yearbook 1952 (London: Baillière, Tindall, & Cox, for the *Medical Press*. 1952. Pp. 360. 17*s*. 6*d*.).—When first looking at a new book, most people skim through the pages, picking out headings and looking at pictures; but this is impracticable here, for the hardiest skimmer is soon deep in the very article, up-to-date and clear, that he has so long been looking for. In a collection of 40 short articles, the editor, Sir Cecil Wakeley, has again succeeded in covering a tremendous lot of ground, and the practitioner, whose daily working ground this is, will welcome these latest maps to help him. Diseases of the skin have appropriately been allotted four articles. Dr. E. J. Moynahan, in an excellent summary of some recent advances in dermatological treatment, makes no bones about penicillin and the later antibiotics. With the exception of tyrothricin and possibly bacitracin, he says, "they have no place as local agents in the treatment of skin disease, because of their very high capacity to produce allergic sensitisation." But not very long ago a persuasive blotter was urging on the practitioner the local application of penicillin in a great many skin conditions. The yearbook will not only keep him fully and accurately informed on the best methods of treatment; it will also encourage him to use only one side of this particular blotter.

THE LANCET

LONDON: SATURDAY, JUNE 21, 1952

Hospital Costing

WHEN the hospitals were taken over by the National Health Service they were in all stages of development. At one end of the scale many of the teaching hospitals provided medical and nursing care of a very high standard, with excellent amenities for patients and staff; at the other end of the scale some of the infirmaries had chronic wards which beggared description; and between these extremes there were hospitals at every intermediate stage. It has always been obvious that, with so wide a diversity, the cost of care in different institutions must vary widely. Hitherto it has not been possible to get a clear picture of the variations, but this becomes somewhat easier now that the Ministry of Health has begun to publish detailed returns.

The first report, which is briefly described on p. 1255, analyses the costs of all the hospitals in England and Wales, under many headings of expenditure representing the running charges (e.g., provisions, laundry, and salaries) and standing charges (e.g., maintenance, rates, printing, and stationery), the analysis including altogether some 31 headings. The result, as may be supposed, is a remarkable document that will be studied carefully by those concerned with hospital administration. But unfortunately there are grounds for thinking that the value of the wealth of detail is not commensurate with the labour involved in its collection. A major difficulty in interpretation at once arises from the compilers' inability to separate the cost of outpatients from that of inpatients. For the purpose of these calculations five outpatient attendances have been counted as the equivalent of one inpatient day; but this is recognised as a questionable assumption, and it is one that almost certainly underestimates the cost of outpatient care. Indeed, a study of the tables shows that satisfactory comparison of inpatient costs in different hospitals will be impossible until outpatients and inpatients are separated. In the London Lock Hospital, for example, the inclusive net cost per bed works out at £111 14*s.* 1*d.* per week; but when allowance has been made for the large outpatient attendances and the low bed-occupancy rate (50%) the adjusted inpatient cost is £17 15*s.* This is still almost £10 a week more than that of another venereal hospital in London (Sheffield Street), where there was a negligible outpatient department, but it would be exceedingly rash, on these figures, to attempt to compare the real inpatient cost in these two hospitals. So it is with many of the teaching and district hospitals where the very large outpatient departments—doubtless run at varying costs—make it hard to place any reliance on the final calculated cost of inpatient care. An accurate allocation of outpatient costs would, we feel sure, bring down the present calculated inpatient cost (on which the charge for pay-beds is calculated). The method now in use is to be deprecated because it works unfairly against hospitals which have improved their consulting clinics and reduced the ratio of old to new attendances: it is unreasonable that hospitals with less efficient and less expensive outpatient departments should be credited with a larger outpatient expenditure, which deceptively decreases the final calculated cost of beds.

Examination of the individual headings in the analysis reveals other fallacies which help to make comparison between hospitals unrealistic. Thus the laundry charges in the specialised hospitals in London range between 18*s.* 9*d.* and 2*d.* per occupied bed per week; and the report does not mention that these figures relate to laundry done by contract only and that the cost of laundry done by the hospital itself is lost in the other headings—e.g., cleaning, other running charges, and non-medical staff. Again, without knowing the number and proportion of resident and non-resident staff, it is impossible to assess the significance of different costs of provisions, which for the London general teaching hospitals range between £3 17*s.* 1*d.* and £1 18*s.* 10*d.* per bed per week. These figures bear no relation to the commonly quoted cost per head, as the following examples illustrate:

Hospital	Weekly cost of provisions per bed as given in report	Actual cost of catering (per person fed)
A	£1 16*s.* 2*d.*	£1 3*s.* 0*d.*
B	£2 1*s.* 4*d.*	18*s.* 2*d.*
C	£2 4*s.* 5*d.*	19*s.* 8*d.*

Equally serious objections can be raised to comparison of maintenance costs, because services not provided on a group basis will be lost under other headings. One wonders, indeed, whether those responsible for making the individual returns were adequately consulted when the survey was originally planned. The analysis of the cost per bed of medical salaries is probably the only column free from any major fallacy; and this gives an excellent picture of the differences in the level of medical staffing in different types of hospital and in different regions.

Despite the defects to which we draw attention, this initial attempt at analysing the cost of the hospital service does in fact provide much information of real importance, and it will stimulate fair criticism and increasing interest in economy in hospital administration. Its main value at present is in allowing some comparison between those hospitals that are generally recognised to be of comparable status—e.g., London teaching hospitals, the former Middlesex county hospitals, or general-practitioner hospitals. It is surprising to note the very large number of hospitals with a bed-occupancy rate of under 85%; and we could wish that the report had given particulars of the average length of stay of patients, which is another index of efficiency in comparing similar hospitals. The administrative problems of a maximum turnover of patients and a high bed-occupancy rate are very complex and would merit the same detailed consideration as has recently been given to outpatient problems by the Nuffield Trust.

Accurate departmental costing of hospital services would entail a biggish increase in administrative staff, which in fact is out of the question. King Edward's Hospital Fund and the Nuffield Provincial Hospitals Trust, are, however, now undertaking a complete unit costing of a small number of representative London and provincial hospitals, and we may hope that their studies will ultimately produce a form of costing suitable for our hospital service, which will supersede the recently introduced, simple, but highly fallacious system of cost analysis of inpatient care.

Herpes Simplex

Studies of the virus of herpes simplex continue to be fruitful but confusing. The primary infection commonly occurs in early childhood and takes the form of acute herpetic stomatitis. Dodd et al.[1] isolated the virus from "aphthous stomatitis," as it was then commonly called; and shortly afterwards Burnet and Williams[2] propounded their conception of the clinical history of the infection, which is now universally accepted. They maintained that herpes simplex is a specific infectious disease with an incubation period of three or four days. After the primary stomatitis the virus becomes latent and the patient non-infectious. Thereafter various exciting agents, such as pyrexia, trauma, and infections, provoke the virus to fresh activity, and the herpetic lesions reappear not as recurrent attacks of stomatitis but as the common mucocutaneous herpes simplex. Only some people are liable to recurrent herpes; and in them, paradoxically, antibodies to the virus are always present. The explanation widely accepted is that in them the virus enjoys a symbiotic existence and stimulates the formation of antibodies. If this primary infection in early life is avoided, the chances of contracting herpes are remote. Subclinical infections must be common, for the majority of adults (65–90%) have serological evidence of previous infection. Primary infection of the adult does take place, but it has only rarely been described. Kilbourne and Horsfall[3] have recorded the case of an adult who had a subacute febrile illness resembling infectious mononucleosis. They infected newborn mice and recovered, not the Coxsackie virus they were seeking, but the virus of herpes simplex. This started two interesting lines of study: (1) the use of the infant mouse for isolating the virus, and (2) the clinical syndromes of primary infection in the adult. They found that the infection was protean in its manifestations. The mouth, tongue, throat, cornea, genitalia, skin, and central nervous system can be affected. In severity the illness varies from a mild stomatitis to an acute inflammation of the brain and meninges; or it may appear as a poorly defined febrile illness as in the case which started them on their investigation.

Primary disease in the newborn is also rare; but it is important since it may take such serious forms as generalised herpes, meningo-encephalitis, or visceral disease, and may cause death. As long ago as 1935 Haas[4] described extensive hepato-adrenal necroses in a premature infant which he tentatively ascribed to the virus of herpes simplex because of the presence of distinctive intranuclear inclusions. Quilligan and Wilson[5] reported a fatality from herpes simplex in a newborn infant whose mother had had herpetic stomatitis immediately before the birth. Necrotic nodules were present in the infant's liver, and virus was recovered from the liver and skin. Zuelzer and Stulberg[6] recently recorded eight cases of fulminating visceral disease and hepatitis in early infancy, from one of which the virus was isolated. Florman and Mindlin[7] describe a case of generalised herpes simplex in an 11-day-old premature infant who developed meningo-encephalitis but survived with neurological defects and chorioretinitis. In the rare instances where a neurotropic strain invades the central nervous system the spread from the portal of entry may be neural or hæmatogenous. van Tongeren and de Jong[8] report a case of encephalitis in which the virus was isolated from the brain, but in which no local lesion of the skin or mucosa was present. The neural path from the local lesion was thought by Goodpasture and Teague[9] to be axonal. The alternative view of Marinesco and Draganesco[10] that spread takes place along the lymphatic spaces of the nerves is not so widely accepted but has received some support from experimental work by Field[11] on herpetic encephalitis following corneal and masseteric inoculation.

There are still plenty of interesting problems connected with the common form of the disease. At the Sundby Hospital in Copenhagen Sylvest[12] found that herpes complicated 1·5% of all medical cases. Among 472 patients with herpes the associated disease was pulmonary (chiefly pneumonia) in 412. So striking was this association that he recommends that "every febrile patient with herpes in hospital ought to undergo a thorough examination of the lungs, including a chest X-ray." The general practitioner, however, meets herpes most commonly as a complication of the common cold; Sylvest had only 7 cases of coryza in his group, and they all had herpes. He also attempted to assess statistically the significance of the dictum, widely credited for a century or more, that herpes simplex is a good prognostic sign in pneumonia. His crude figures confirmed this dictum, for deaths among his cases with herpes amounted to 4%, compared with 15·6% in those without herpes. But was the pneumonia with herpes a different disease from the pneumonia without herpes? Confusion was quite possible; for primary atypical pneumonia, if it existed at that time, must have been included unknowingly with pneumonias of a different prognosis. From epidemiological similarities Sylvest decided that the pneumonia with herpes was not a separate disease. He could find no statistical support for the possibility that it was the temperature rather than the pneumonia which was the determining factor. His figures had to be corrected for age; for herpes is commoner in young and middle-aged people, in whom pneumonia is less fatal. He also had to consider whether pneumonia could kill the patient before herpes had time to appear. Herpes commonly appears on the 2nd to 7th day of the illness, and pneumonia usually kills between the 4th and 8th day, so that some patients who died might have had herpes if they had survived. A statistical correction was therefore necessary. Treatment of pneumonia improved enormously over the period of the investigation (1933–44), and the figures had to be broken down into three therapeutic periods before they could be compared. When all corrections were made there still remained evidence of the inexplicable better prognosis of patients with pneumonia who develop herpes.

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[1] Dodd, K., Johnston, L. M., Buddingh, G. J. *J. Pediat.* 1938, 12, 95.

[2] Burnet, F. M., Williams, S. W. *Med. J. Aust.* 1939, i, 637.

[3] Kilbourne, E. D., Horsfall, F. L. *Arch. intern. Med.* 1951, 88, 495.

[4] Haas, G. M. *Amer. J. Path.* 1935, 11, 127.

[5] Quilligan, J. J., Wilson, J. L. *J. Lab. clin. Med.* 1951, 38, 742.

[6] Zuelzer, W. W., Stulberg, C. S. *Amer. J. Dis. Child.* 1952, 83, 421.

[7] Florman, A. L., Mindlin, R. L. *Ibid*, p. 811.

[8] van Tongeren, H. A. E., de Jong, J. G. Y. *Ned. Tijdschr. Geneesk.* 1952, 96, 871.

[9] Goodpasture, E. W., Teague, O. *J. med. Res.* 1923, 44, 139.

[10] Marinesco, G., Draganesco, S. *Ann. Inst. Pasteur.* 1923, 37, 753; *Rev. Neurol.* 1932, 1, 1.

[11] Field, E. J. *J. Path. Bact.* 1952, 64, 1.

[12] Sylvest, O. *Acta med. scand.* 1952, 141, 385.

Cancer of the Breast

EACH year some 8000 people in England and Wales die of cancer of the breast; and the chance that a woman of 40 will eventually die of this cause is about 3 in 100. The editorial board of the *British Journal of Radiology* has therefore done well to devote a supplement to a review of the clinical, pathological, and statistical aspects of this disease. Here Prof. WALDRON SMITHERS and his colleagues[1] have collected data about the 1777 new cases seen at the Royal Cancer Hospital, London, in the years 1937–48, and compared these with other reports from this country, Europe, and the U.S.A.

Professor SMITHERS and his associates say that the prognosis depends fundamentally on the characteristics of the individual tumour. Thus tumours of short duration but with great potentialities for spreading are less amenable to treatment than those of longer duration but local type. Furthermore tumours of the medial half of the breast are more serious than those of the lateral half. But how are we to assess the growth potentialities of a tumour before treatment is started, and how should this assessment influence treatment? SMITHERS et al. plead for more accurate clinical staging, preferably in five stages, which should be defined by international agreement as has been done with carcinoma of the cervix uteri. They argue that in experienced hands clinical staging is more accurate than pathological staging, unless this is done with a care and accuracy that is almost beyond the scope of normal pathological practice. Clinical staging, moreover, can be done before treatment is started; whereas pathological staging is not so much a guide to treatment as a comment on the wisdom of treatment already undertaken and a prediction of its outcome.

With regard to treatment SMITHERS et al. advocate a more flexible plan which should be fitted to the individual case, rather than either routine radical mastectomy or routine local mastectomy followed by irradiation of the axilla. Hormone therapy they would reserve for the palliation of cases unsuitable for operation. Reported results, they point out, are seldom easily compared; and they would like to see these presented in an internationally agreed way. Nevertheless they are satisfied that over the years survival-rates have steadily improved. McKINNON,[2] on the other hand, believes that early treatment, whether by irradiation or operation, cannot obviate the lethal spread of breast cancer by the blood-stream, and therefore cannot materially reduce mortality or postpone death; and he attributes so-called cures by early treatment to the inclusion of borderline cases. Similarly PARK and LEES[3] contend that there is no proof that the five-year survival-rate of patients with breast cancer is affected by treatment.

Professor SMITHERS and his colleagues have been engaged for many years on their thought-provoking review, which raises many issues. They take no account of the disability inherent in modern therapeutic methods, though indeed this factor would not readily lend itself to statistical analysis. If, instead of radical mastectomy, we recommend irradiation of the axilla, does the patient suffer more or less disability? Again, would medicine be better served if more pathologists gave their time to investigating each mastectomy specimen received from the operating-theatre instead of doing the wholesale chemical and hæmatological tests commonly demanded for patients in the medical wards? The time is ripe for a national stocktaking of this common, distressing, and killing disease.

Annotations

EFFECTS OF ARTERIAL ARREST

TEMPORARY arrest of the arterial supply is a necessary part of many surgical procedures. In situations such as the thoracic aorta and the internal carotid artery, severe damage rapidly develops. The kidney and the gut are rather less sensitive to temporary arterial interruption; and under favourable conditions the limbs—particularly the upper limbs—will tolerate prolonged ischæmia. Tourniquets are, however, highly dangerous because they are so often misused. Most war surgeons remember cases in which a limb was lost owing to the unnecessary application of a tourniquet. Even in the calmer routine of peace-time operations, disaster sometimes overtakes the surgeon with responsibility for removing the tourniquet. When the mistake is recognised and the constriction is released, severe shock develops along with disorganisation of the limb tissues. Renal failure (the so-called "traumatic uræmia") ensues. In this commonly fatal condition tubular necrosis is associated with anuria, though the blood-pressure returns to its normal level and often exceeds it. Toxic intracellular products accumulate in the blood; potassium is one now easily estimated. Early amputation and feeding with nitrogen-free nutrients by a gastric tube may save more of these patients in future.

Less is known of the response to arterial arrest in some other structures. Permanent division of the hepatic artery is usually followed by massive infection of the liver with organisms borne to it by the portal system; but systemic penicillin may delay or even prevent this invasion.[4] The cirrhotic liver, it seems, responds differently, especially to Hunterian ligation (above the gastroduodenal branch). Berman et al.[5] have suggested that this operation may be effective in the treatment of ascites.

Damage to the testicular artery is a common accident during operations involving the spermatic cord, either in the abdomen or in the groin and scrotum. Mobilisation of the ureter or the colon, orchidopexy, or the excision of a hernia or varicocele all threaten the blood-supply of the testis. If swelling or pain develops, venous thrombosis will probably be blamed; less dramatic signs would hardly be thought to herald a serious complication, yet there is new evidence that they may. Oettlé and Harrison[6] have studied the effects of experimental arrest of the testicular arterial blood-supply in rats. The ligature was applied either (*a*) below the anastomosis with the artery to the vas deferens, which is at the lower pole of the testis, or (*b*) to the proximal part of the vessel within the abdomen. After permanent ligation by the second procedure the volume of the testis was reduced by a half within 2–4 weeks. The thickness of the tunica albuginea increased about six times, and nothing of the normal tubular or interstitial structure remained except for a few scattered remnants close to the surface which may have obtained nutrition by diffusion. Temporary arrest of the arterial supply for even an hour led to serious and irrecoverable damage to the spermatogenic pattern, while longer interruption was followed by complete tubular destruction.

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[1] Cancer of the Breast: a review. By D. W. SMITHERS, P. RIGBY-JONES, D. A. G. GALTON, and P. M. PAYNE. *Brit. J. Radiol.* 1952, suppl. no. 4.

[2] McKinnon, N. E. *Canad. J. publ. Hlth*, 1951, 42, 218.

[3] Park, W. W., Lees, J. C. *Surg. Gynec. Obstet.* 1951, 93, 129.

[4] Markowitz, J., Rappaport, A., Scott, A. *Amer. J. digest. Dis.* 1949, 16, 344.

[5] Berman, J. K., Koenig, H., Muller, L. P. *Arch. Surg.* 1951, 63, 379.

We must now consider the possibility of this serious hidden complication after surgical dissection of the spermatic cord. Such is the sensitivity of the seminal epithelium to ischæmia that even temporary arrest of its circulation may result in irreversible damage, which is not suspected because there is no pain or swelling or later shrinkage of the testicle. There is clear evidence, too, that despite complacent opinions to the contrary the collateral circulation to the testicle after ligation of its main artery is quite inadequate for survival of functioning cells.

SELENIUM AND DENTAL DECAY

THOSE who vehemently oppose addition of fluorine to our water-supplies will be disturbed to hear that the effects of other trace elements on dental caries are being investigated. But one at least of these, selenium, seems to have nothing to recommend it.[7] Indeed a case could be made out for removing it from those waters in which it is naturally present—a proposal that would give an interesting twist to the controversy on the ethics of interfering with the water provided by Nature.

Selenium is thought to be a normal constituent of certain soils, from which it is absorbed by growing vegetation, and it has been found in many cereal crops. It can be detected in human urine, and estimations of its excretion are used as the most reliable guide to the amounts taken in the diet. The effect of selenium on cattle has attracted considerable attention, and, though its effect in man has still to be fully explored, some interesting work has been done, however, in the United States.

In the State of Oregon there are two counties called Clatsop and Klamath. The children of Klamath have the best teeth in the State, but those of Clatsop have the worst. Dentists are no fewer in Clatsop than in Klamath; there is just as much fluorine in its water; and the tuck-shops sell no more "candy bars and carbonated beverages" than the shops of Klamath. Indeed it was difficult to explain the difference, though possibly less sunshine may have had something to do with it. But when the excretion of selenium in 24 boys and girls from Clatsop was compared with that in 29 from Klamath, it was found that the children born and bred in Clatsop county had more selenium in their urine. Though much more work must be done before the connection is proved, this little survey does suggest that selenium makes teeth more liable to decay. Smith et al.[8] found that people living in areas where the soil was relatively rich in selenium also had remarkably bad teeth.

There is strong evidence that an enhanced resistance to dental caries is conferred by waters containing fluorine (even as little as 1 part per million), as Mackenzie has lately shown in a convincing judgment.[9] These observations on selenium merely emphasise that our understanding of the processes of decay is far from complete, and they certainly do nothing to weaken the case for fluorine.

IMPACT OF SCIENCE ON LITERATURE

W. N. P. Barbellion, the biologist whose diary recorded a conflict between the profession of science and the lure of literature, wrote in his last days with his familiar flash of energy: "Rupert Brooke said the brightest thing in the world was a leaf with the sun shining on it. God pity his ignorance! The brightest thing in the world is a Ctenophor in *a glass jar standing* in the sun. This is a bit of a secret, for no one knows about it save only the naturalist." So, the profession of science might be of peculiar advantage to the literary expression of the magic of life. And yet elsewhere Barbellion, whose temperament has been likened to that of Keats, declared with Keats that the scientist's kind of truth destroys the pleasures of [illegible] the pearl in the oyster-shell to [illegible]

It is the faith of many that life without the spirit of wonder would be worthless; it is their fear that the analysis of its pageantry must produce a clever barbarism, and an inglorious end to that. There is evidence enough in literature that the scientific mind does not invariably, by acquiring part of Nature's secrets, rob them of beauty or fail in uttering the beautiful which it then unveils. But the party that takes Coleridge's definition of science (and not prose) as the antithesis of poetry will not be comforted. It stares past the instances of affinity between, let us say, Newton and Shelley, or *The Ancient Mariner* and *The Origin of Species*, and is frightened by a phantasm of the coming race as metallic, *unspiritual, sensual, omniscient, and knowing nothing.*

The literary man, it may be said, is not usually charitable to the scientist; he has been checked, perhaps, in a moment of intended fraternisation by the technical appalments of the scientist's particular study. He periodically reads what the scientist with the brilliant easy style can tell him, and may then work a theory or a fact into his own commentary on things as they are, things as they might be. The poetry of Thomas Hardy, who certainly honoured both by study and with admiration the servants of "philosophy" in the full meaning of the word, is an example to all writers and investigators. Hardy's lyrics are often a vigorous variation of philosophical transactions. But then Hardy's intellectual capability and artistic originality are seldom found either separately or harmonised as in him.

At least this age is tackling this vexed question in a fashion claimed to be typical of our modernity. America is not going to leave the case undocumented, at least. Such is the *starting-point* of a clearly and impartially written sketch of the Impact of Science in Literature by Professor Dudley.[10] Since 1939, he observes, "a group to study the relations of literature and science" has been at work "within the Modern Language Association of America," and the compilations and dispositions of these scholars are now becoming annual productions. Dudley regards the effort as promising to influence the literary man rather than the scientist; and, if the new Coleridge cannot readily become the comprehending associate of the new Humphry Davy in the daily round, still the plan may help.

But Providence cantankerously retains a share in the arrangements concerning even the intercourse between science and literature. Another question affecting the future is what children are born. It is really not so long since H. G. Wells was an infant, over whom the

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6. Oettlé, A. G., Harrison, R. G. *J. Path. Bact.* 1952, 64, 273.
7. Hadjimarkos, D. M., Storvick, C. A., Remmert, L. F. *J. Pediat.* 1952, 40, 451.
8. Smith, M. I., Franke, K. W., Westfall, B. B. *Publ. Hlth Rep., Wash.* 1946, 51, 1496.
9. Mackenzie, E. F. W. *Lancet*, May 10, 1952, p. 961.
10. Dudley, F. A. *Science*, 1952, 115, 412.

angel of scientific romance may be allowed—despite modern poetry—to have hovered smilingly. Lucretius had had the same protection somewhat earlier. The battle between the prejudices for and against the scientist in respect of the soul of man, it seems, is now and then settled in the arrival of the right genius. Robert Bridges, physician, was able to cultivate his garden in easy unity with Robert Bridges, poet.

PHARMACOLOGY OF ANTABUS

THE introduction of 'Antabus' (tetraethylthiuram-disulphide) seemed to be a real advance in the treatment of chronic alcoholism. Nevertheless, all who have applied this treatment have emphasised the possible dangers of the antabus-alcohol reaction. Hine et al.[1] have now correlated the clinical manifestations of this reaction with blood-alcohol and blood-acetaldehyde levels. They find that antabus does not affect the rate of absorption, the blood level, or the rate of metabolism of alcohol. They confirm that the symptoms of an antabus-alcohol reaction are due to a distinct increase in the blood-acetaldehyde level. This, they suggest, is due to the inhibition of aldehyde oxidation. Particularly significant is their observation that antabus raises the blood-acetaldehyde level above normal even in those who have not consumed any alcohol. Clearly it is no longer possible to think of antabus as inert except when associated with alcohol.

Usually most of the symptoms and signs of an acute antabus-alcohol reaction reach a peak at the same time as the blood-acetaldehyde level: but this is not always so. Hine et al. noted in some patients an early atypical reaction without an appreciable rise in the acetaldehyde level. Other patients reported unpleasant symptoms several hours later, long after the blood-acetaldehyde had returned to normal. Hine suggests that other and unidentified toxic factors may operate in these cases. The most dangerous complication in an antabus-alcohol reaction is a sudden fall in blood-pressure, which is often accompanied by a fall in pulse-rate. It would seem that acetaldehyde has a direct toxic action on the myocardium. An antabus test should not be carried out if there is any reason to believe that the myocardium is diseased.

Now that the biochemistry of the antabus-alcohol reaction is better understood, we must hope that the more serious features of the reaction will be controlled. Oxygen, intravenous vitamin C, and parenteral ephedrine sulphate have been said to relieve the acute reaction[2]; and it would be worth studying the effect of each of these remedies on the blood-acetaldehyde level.

INTERNATIONAL REGULATIONS FOR OCCUPATIONAL DISEASES

THE 35th session of the International Labour Conference, which began in Geneva on June 4, is to discuss a report which gives the opinions of thirty-six nations about the control and prevention of occupational diseases. Replies to a questionary sent to the governments (including Poland, China, and Yugoslavia) were unanimous about the need for international regulations and for compulsory notification of occupational diseases. Some governments said that the I.L.O. should prepare a schedule of notifiable diseases and at the same time should outline the measures necessary to prevent or reduce them. Thirty-one governments said that the regulations should take the form of a recommendation, while others were in favour of drawing up an international Convention, which is more binding. The I.L.O. has previously adopted conventions and recommendations in the field of occupational health, such as the White Lead Convention. The proposed new regulations enlarge the scope of these conventions and recommendations by emphasising the preventive aspects. Most of the countries replying to the questionary said that the new regulations should be made elastic enough to cover not only the known occupational diseases but also those which might arise from new processes.

The replies cited the well-known occupational diseases and also some of the less-known health risks. Most governments laid stress on the damaging effects on health of noise, glare, vibration, dust, contaminated air, heat, and fumes and odours in the workplaces. The preventive measures listed follow the usual pattern, but it is emphasised that employers should provide protective clothing and equipment for workers in certain dangerous processes. The proposed regulations also provide for initial and periodical medical examinations of workers engaged in occupations involving special risks. The examinations should be made without charge to the workers. The national schedules of notifiable occupational diseases vary so much in length and detail that we welcome this international attempt to bring order into the House of Babel.

MONILIASIS

Candida albicans, a common saprophyte, occasionally becomes pathogenic. The best known of the lesions which it may produce are those affecting the skin and mucous membranes of the mouth and vagina. But pulmonary moniliasis is also a recognised entity; and since it was first described by Castellani[1] in 1905 accounts of it have come from most parts of the world and especially tropical countries. The condition, when severe, may give rise to a clinical picture very similar to that of pulmonary tuberculosis, with productive cough, sometimes hæmoptysis, fever, sweating, and wasting. Infiltration of the lungs, unilateral or bilateral, is followed by cavitation and fibrosis. Meningitis due to moniliasis was first reported by Smith and Sano[2] in 1933; monilial subacute endocarditis is found occasionally[3,4]; and the fungus may rarely spread to the blood-stream.[5–7] Lately moniliasis has come into prominence because it sometimes complicates treatment with the antibiotics—particularly aureomycin, chloramphenicol, and terramycin. The lesions produced in this way affect mainly the gastro-intestinal tract,[8] but death from pulmonary moniliasis following intensive antibiotic therapy has been reported by Ormerod and Friedmann.[9] It is also significant that of four debilitated infants with enterocolitis who are reported to have died of systemic mycosis three had received penicillin.[7]

On earlier pages of this issue we publish reports of moniliasis pneumonia following aureomycin therapy, and of moniliasis of the urinary tract following administration of chloramphenicol. In the case described by Squadron-Leader Wolff, the patient was being treated for bilateral basal pneumonia, and the course of events is clearly traced by the change in flora of the sputum while he was receiving aureomycin and streptomycin. *Hæmophilus influenzæ* and pneumococci were replaced by large numbers of yeast-like organisms, which on culture resembled *C. albicans*. During the antibiotic therapy the patient's condition deteriorated and cavities appeared in the upper lobe of the right lung; but his condition improved rapidly soon after the antibiotics were discontinued. In the case reported by Mr. Taylor and Dr. Rundle, the relation between the moniliasis of the urinary tract and the antibiotic therapy is less certain. The diagnosis of the disease which led to

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1. Hine, C. H., Burbridge, T. N., Macklin, E. A., Anderson, H. H., Simon, A. *J. clin. Invest.* 1952, 31, 817.
2. Report of the Council on Pharmacy and Chemistry: Antabuse (disulfiram) in the Treatment of Alcoholism. *J. Amer. med. Ass.* 1952, 149, 275.

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1. Castellani, A. Ceylon Medical Reports, 1905.
2. Smith, L. W., Sano, E. M. *J. infect. Dis.* 1933, 53, 187.
3. Joachim, H., Polayes, J. H. *J. Amer. med. Ass.* 1940 115, 205.
4. Pasternack, J. G. *Amer. J. clin. Path.* 1942, 12, 496.
5. Lederer, H., McLaren Todd, R. *Arch. Dis. Childh.* 1949, 224, 200.
6. Wessler, S., Browne, H. *Ann. intern. med.* 1945, 22, 886.
7. Dubiz, J. V., Mead, M. *Med. J. Aust.* 1951, i, 179.
8. See *Lancet*, Feb. 16, 1952, p. 352.
9. Ormerod, F. C., Friedmann, I. *Brit. med. J.* 1951, ii, 1439.

admission is not known, and there is no initial report on the urine or blood-urea for comparison. What is certain is that, during treatment with chloramphenicol for an acute febrile illness of unknown origin, suppression of urine developed; and, despite a short remission on the 11th and 12th days, when there was diuresis, the patient died of uræmia. *C. albicans* was cultured from the urine, the bladder, and both ureters; and at necropsy the patient was found to have pyelonephritis and blockage of both renal pelves and ureters by *C. albicans*. Mr. Taylor and Dr. Rundle believe that temporary diuresis in the course of otherwise progressive anuria may be diagnostic of such a blockage.

These two cases illustrate that rarely the complications of antibiotic therapy may be dangerous. Two precautionary measures might be suggested. First, before starting therapy with aureomycin, chloramphenicol, or terramycin, it is wise to ascertain, whenever possible, the bacteriology of the condition (where it is desirable to start treatment before the bacteriological report is known, penicillin or sulphonamides can be used in the first instance); and it is also best to check periodically the bacterial flora while the patient continues to receive the antibiotic. Secondly, it would seem inadvisable to persist with an antibiotic when a patient is not responding to it. If in the course of five days there is no obvious improvement and the temperature has not fallen, the antibiotic should be stopped and different treatment instituted.

INTRAHEPATIC OBSTRUCTIVE JAUNDICE

THE diagnostic problem in cases of non-hæmolytic jaundice may occasionally prove insoluble, despite help from liver-function tests. Since the treatment of biliary obstruction is esse[illegible] [illegible]ile that of parenchymal hepatitis is [illegible], a correct solution is obviously important. A common cause of confusion is damage to the liver cells from long-continued biliary obstruction, so that clinical and laboratory signs of parenchymal liver damage come to overlie the original picture of obstruction. This is especially likely to happen when infection and inflammation arise in the obstructed biliary passages. Until recently less attention was paid to the opposite state of affairs, in which features of obstruction become dominant in subsequently proved cases of parenchymal hepatitis. Of 228 cases of hepatitis reported by Steigmann et al.,[1] 65 at the time of admission showed evidence of severe interference with the bile-flow, such as a serum-alkaline-phosphatase above 15 Bodansky units, a total serum-cholesterol above 300 mg. per 100 ml., or a urinary urobilinogen content of less than 1 mg. per 24 hours. The change underlying these obstructive phenomena is still uncertain; but Watson and Hoffbauer[2] have suggested that it may be excessive permeability of the cholangioles with the result that the bile will leak back into the circulation.

That intrahepatic cholangiolitis, due probably to a low-grade infection, can produce such a clinical picture is now usually agreed; but this should not cause the much commoner condition of biliary obstruction in the porta hepatis to be overlooked. Two cases reported by Billington[3] illustrate how easy it is to miss the diagnosis of this condition. The first case was in a man of 60 with a typically obstructive form of jaundice, in whom no extrahepatic lesion of the biliary ducts was detected despite two laparotomies. At necropsy about nine months after the onset of jaundice, no occluding lesion was found until section through the porta hepatis, which appeared normal from outside, revealed stenosis of the common hepatic duct due to an early duct carcinoma. In this case, owing to an anatomical variation from normal, the junction of the right and left hepatic ducts took place within the liver, and consequently quite a small intrahepatic neoplasm could interrupt the entire biliary outflow. In the second case, where the more usual arrangement of the duct system was present, an almost identical clinical picture was produced by an intrahepatic primary adenocarcinoma of the left hepatic duct with secondary biliary cirrhosis confined to the left lobe of the liver.

From these, and many other similar cases,[4,5] it is evident that, in cases of obstructive jaundice, negative findings at a simple exploratory laparotomy cannot be taken to exclude a localised lesion in the duct system. Cholangiography at the time of operation[6] seems to be the only means by which these cryptic obstructions might be recognised during life. Although radical extirpation would rarely be feasible, it is obviously unsatis-[illegible]

BRAILLE CENTENARY

Louis Braille was the son of a French saddler. At the age of 3, while playing with his father's awl, he damaged an eye, and shortly afterwards he became totally blind. He entered the only school for the blind then existing in France, where he quickly absorbed such knowledge as lay open to him, but his active mind, irritated by the tedious method of reading by touch that was then in use, longed for more. How could he learn all that he wanted to know when one word might take up several lines, and a textbook twenty large volumes? While Louis was still a boy, a retired officer of the French artillery came to the school to tell the pupils about the *écriture nocturne* that he had devised to enable soldiers to send messages in the dark. The blind boy knew at once that these embossed dots would rid him of frustration, and from that day he worked tirelessly to simplify and perfect a system for the blind. How well he worked he never knew; for, despite a successful demonstration of his type in Paris in 1834, the governors of the school were unwilling to adopt it. Some years later this decision was reversed, but by then Braille was dying of tuberculosis, and when he died on Jan. 6, 1852, at the age of 43, his hopes that all blind people might one day read and learn his way seemed vain. And yet today the name of this great man and the feel of his type are known throughout the world.*

The centenary of Braille's death is being marked in London by an exhibition which was opened by the Duke of Edinburgh at the National Institute for the Blind, Great Portland Street, W.1, on June 11. The exhibition, which is open until July 5, also honours the memory of Dr. Thomas Armitage, who worked long and successfully to establish the Braille system for the English-speaking blind. A new machine is on view which, it is hoped, will revolutionise the printing of Braille. Plastic dots are used instead of the usual embossed ones, which means that the type is much more clearly defined and durable than it was with the old method. Moreover, both sides of the paper can be used, and the paper itself need not be so thick as that used for embossing. This machine, with its cheap and rapid output, promises to make books for blind hands to read in greater number and variety than Braille could ever have hoped for.

AT the fifth World Health Assembly held in Geneva last month, Dr. BROCK CHISHOLM was invited to postpone his retirement, in July, 1953, from the post of director-general of the World Health Organisation. He was asked to say, by the end of this year, whether he will be able to accept a further term of office.

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[1] Steigmann, F., Meyer, K. A., Popper, H. *Arch. Surg.* 1949, 59, 101.

[2] Watson, C. J., Hoffbauer, F. W. *Ann. intern. Med.* 1946, 25, 195.

[3] Billington, B. P. *Med. J. Aust.* May 7, 1952, p. 663.

[4] [illegible] Lectures on the Liver and its Diseases, [illegible]

[5] [illegible] *Med. J.* 1951, 5, 321.

[6] [illegible] June 7, 1952, p. 1153.

* The account of Braille's life is abridged from an article by J. de la Mare Rowley in Summer, 1952, issue of *Social Service: a Quarterly Survey.*

Special Articles

A GERIATRIC HOSPITAL SERVICE

WILLIAM HUGHES
M.D. N.U.I., M.R.C.P.
AREA GERIATRICIAN

S. L. PUGMIRE
L.R.C.P.I.
MEDICAL OFFICER

STAPLETON HOSPITAL, BRISTOL

IT might be argued that there is nothing new about a geriatric service—that a humanitarian "service" which looks after the aged sick has been inherent in all civilisations. In this country statutory provision for the destitute of all ages goes back to Elizabethan times. The evolution of the old poor-law, and the modern health services in so far as they affect the aged sick, has been recently described by Amulree (1951). Most people are now familiar with the crude statistics of the position. The relative number of old people in the community has increased and is increasing. The improvement in public health and advances in preventive and curative medicine have combined to prolong the average survival-rate and upset the balance of the population. The fall in the infant-mortality rate has not offset the results of the declining birth-rate. The emigration of young adults means a net loss in the wage-earning groups and a relative increase among non-earners. Some of the salient features of the present position and recent trends are illustrated in table I.

TABLE I—AGE-DISTRIBUTION OF THE POPULATION OF GREAT BRITAIN 1851 TO 1947 AND PROJECTED TO 1977

	No. per 1000 population in each age-group (years)		
Date	0–14	15–64	Over 65
1851	355	598	47
1891	351	601	48
1911	308	639	53
1947	215	681	105
1977*	194	646	160

* Projected, assuming family size constant at the same level as among couples married 1927–38; marriage rates constant at "intermediate" level of 1942–47; mortality falling and no net migration (Royal Commission on Population Report, 1949).

The area catered for by the South Western Regional Hospital Board has a total population of some 4 million and can expect an increase of nearly 7000 aged per annum. The region is divided into five clinical areas. The Bristol clinical area has a population estimated at 650,000.

The increase in the number of old people is a social problem and it is with the impact of the problem on medicine—inside and outside hospitals—that we are concerned. We cannot divorce the social problem from the hospital problem: experience shows that elderly patients are rarely admitted to hospital for clinical reasons only. We propose to describe what has been done so far to cope with the geriatric problem in Bristol hospitals, to compare our development with what has been done in other areas, and to discuss the many difficulties which arise.

The Geriatric Centre

On the appointed day in 1948 the main concentrations of aged sick in the Bristol clinical area were housed in 9 public-assistance institutions. Of these, 5 were designated hospitals and 4 "joint-user" institutions. At the end of 1949 one of us (W. H.) made a preliminary survey of 6 of these institutions; 3 more were surveyed at a later date. The results are shown in table II.

As a first step it was decided to recommend the setting up of a geriatric centre in the largest of the Bristol City institutions—Stapleton Hospital—to deal with the problems of the clinical area. This recommendation was accepted in principle by the Regional Hospital Board and by the hospital management committee concerned.

The basic idea was to establish a centre to deal with the clinical problems of the whole area. This was more ambitious than the setting up of a geriatric unit. Other geriatric units throughout the country, and particularly those in the London area, had shown what could be done for the individual case (Warren 1943, 1948, Cosin 1948). Brooke (1949) had shown that geriatrics need not be confined to the hospitals; and the extramural development of geriatrics had been particularly emphasised in America by Bluestone (1949). Wilson (1952) had already established a scheme in Cornwall which catered successfully for the geriatric needs of the whole clinical area.

The first step in the development of Stapleton Hospital was the allocation of a block of 120 beds for a geriatric unit. By a process of internal transfers these beds were filled with acute cases and cases considered worthy of further investigation with a view to discharge. Here the necessary sorting and classification of the inmates could be carried out. All new admissions were directed to the unit for screening and preliminary treatment. Although the hospital lacked X-ray apparatus and laboratory facilities, there was scope for expansion without major structural alterations, and laboratory and X-ray facilities are available at a neighbouring hospital. This allowed us to admit the most urgent cases on the waiting-list while continuing to study the general problem. Beyond this point our path has been beset with difficulties, most of which must be recognised as inherent in the geriatric situation in any large city.

CLASSIFICATION OF PATIENTS

The first major difficulty arose after we had classified the inmates in Stapleton Hospital. On paper there were at least four categories for disposal—mental defectives, psychotics, ambulant, and frail ambulant. When it came to doing something practical, the categories dissolved quickly into individuals, all of whom had certain rights to be considered. In most cases the inmates did not wish to be transferred or discharged. Many had relatives who were strongly opposed to interference. Two of the categories came under statutory control—mental defectives and psychotics. Then it was found that many of the inmates who had been in the institution for years were mental defectives, although it would not now be practical to have them "ascertained" as such.

Mental Defectives

The magnitude of the mental defective problem is peculiar to this area: before 1948, Bristol catered for

TABLE II—CLASSIFICATION OF PATIENTS IN 9 PUBLIC-ASSISTANCE INSTITUTIONS IN 1949

Patients	City hospitals			Country hospitals						
	Stapleton*	Snowdon*	Eastville†	Thornbury*	Keynsham*	Wells*	Clutton†	Ridgewood†	Ilex Lodge*	Total
Frail ambulant	448	54	0	22	4	17	3	2	4	554
Ambulant ..	208	50	14	28	31	26	34	20	14	425
Bedfast ..	154	152	106	51	33	15	25	27	34	597
Acutely ill ..	30	38	21	11	17	11	4	3	0	135
Total ..	840	294	141	112	85	69	66	52	52	1711

* Regional Hospitals Board hospitals. † Joint-user institutions.

All these institutions contained a mixed population of sick and destitute. In the joint-user institutions the beds were divided between the Regional Hospitals Board and local authority, the major user taking over the day-to-day management.

these cases for the surrounding counties, and all the available institutions were already full. It has been found possible, however, to place a few at a time in other institutions with the result that the numbers of "ascertained" defectives in Stapleton have diminished from 75 males and 84 females, in 1949, to 34 males and 26 females now.

Psychotics

The psychotics did not present so much difficulty. Many of them were old enough to be regarded as "senile dements" and decertified. Those with serious disorders of behaviour were gradually transferred to the mental hospital in exchange for docile or bedfast aged psychotics who became "senile dements." The numbers under section 16 of the Lunacy Act have thus shrunk from 283 to 44. The hospital is still left with the admission wards under section 20 of the Lunacy Act, but the patients admitted are not objectionable; indeed many are aged sick and not a few are sent in by doctors because this is the only way of obtaining a bed quickly. During the past year over 100 patients found their way to the geriatric wards by this route.

Ambulants

The aged unascertained mental defectives—the old "workhouse type"—and the aged ambulants, with a memory defect or a mild degree of mental deterioration, form a category which is difficult to dispose of. We cannot help feeling that they should not occupy hospital beds. On the other hand, it must be admitted that they are unsuitable for the new type of hostel which is evolving under the control of the local authority. The inmates have become "residents," and many of the old people are there not because they are destitute but because they cannot get domestic help. Local-authority officers complain when we send them these mentally infirm old people. The latter fitted into the pattern of the workhouse but not the modern hostel. After further examination 151 persons of this group could be classified as shown in table III. Not all were old; 48 were under 60. There were 11 aged 30–39, 15 aged 40–49, 22 aged 50–59, 31 aged 60–69, 50 aged 70–79, 20 aged 80–89, and 2 over 90.

It is now well recognised that disease and infirmity in the aged rarely arise from a single cause (Thomson 1949). In working out a classification of this type of patient it is often found that clinical diagnosis is less important than behaviour. Thus a rigid classification on clinical grounds would separate schizophrenics, epileptics, and mental defectives, but in the wards we have found it essential to group them according to their social behaviour. The ambulants were therefore classified from this point of view for the purpose of disposal.

The Frail Ambulants

To define a frail ambulant we need social as well as clinical coördinates. Clinically, the old person of this type is incapable by reason of mental or physical infirmity of looking after himself, but at the same time he is not in need of skilled medical or nursing attention and is not certifiable. Socially, there is no relative or friend able and willing to look after him.

More and more we are becoming convinced that in the frail ambulant we come up against the major geriatric problem of our times. At first sight it appears extraordinary that no special provision has been made for the group in recent social legislation. The aged sick are catered for under the National Health Service Act. Destitute old people come under Part 3 (sections 21 and 22) of the *National Assistance Act of 1948*. *The interests of the frail-ambulant group have been adversely affected by this division of responsibility under the National Health Service and National Assistance Acts.* The tendency among many local authorities to separate the administration of their welfare and health departments has made matters worse. In practice this means that a consultation between the doctors of the two authorities will not finally decide whether a frail ambulant is admitted to a hostel or not; the final decision rests with the welfare department of the local authority.

It will be readily understood that in such circumstances awkward and embarrassing situations can arise. Thus in more than one instance, an old person transferred to the hostel, after multiple consultations involving doctors, relatives, and lay administrators, has been known to develop a fatal coronary thrombosis or stroke within a few days of discharge. It is not enough to argue that it is impossible to forecast the incidence of stroke and coronary thrombosis or that hospital beds must be freed for the admission of urgent cases. *We must continue to press for legislation which will bring this intolerable situation to an end.*

TABLE III—CLASSIFICATION OF 151 UNASCERTAINED MENTAL DEFECTIVES AND SOCIAL CASES

Clinical classification		Behaviour classification	
Unascertained mental defectives	36 (*24%*)	*Suitable for hostel:* ..	51 (*34%*)
Low normal ..	26 (*18%*)	Good workers ..	12 (*8%*)
Senile dements ..	35 (*24%*)	Always well-behaved	22 (*14%*)
Mild paranoid ..	19 (*12%*)	Behaviour variable	17 (*12%*)
Mild schizophrenics	19 (*12%*)	*Not suitable for hostel:*	100 (*66%*)
Postencephalitics ..	10 (*6%*)	Needing supervision	44 (*29%*)
Epileptics	6 (*4%*)	Needing help at toilet, &c.	15 (*10%*)
		Bad-tempered ..	19 (*12%*)
		Trouble-makers ..	10 (*7%*)
		Dirty habits ..	12 (*8%*)

TABLE IV—HOSPITAL POPULATION IN 1951 AND 1952

Class of patient	Beds occupied daily		Bed gain or loss
	1951	1952	
Sick, frail ambulant, awaiting discharge	*411*	*363*	−48
Permanent bedfast	130	232	+102
Certified:			
Under M.D. Act	128	67	−61
Under Lunacy Acts	118	44	−74
Ambulant epileptics	30	19	−11
Ambulant intractable senile dements. ..	23	0	−23
Total	840	725	−115

REDISTRIBUTION OF THE HOSPITAL POPULATION

In the process of reorganising the hospital we came to realise that in the past it had provided dormitory accommodation for a largely ambulant population. To convert these dormitories into wards will entail heavy capital expenditure. The management committee have found it possible, however, to carry out a modified programme of repairs and decoration which will allow most of the dormitories to function as wards, but this programme has resulted in a net daily loss of 115 beds, as shown in table IV.

During 1951 we were able to review the whole population of the hospital. Any patients that we considered might benefit from treatment were transferred to the unit for screening. We got on with the task of getting relatives, local authorities, and voluntary bodies to help in the disposal of the ambulant and frail-ambulant population. Since many had no relatives and since the resources of voluntary organisations are very limited, the main burden fell on the local authorities. They coöperated as far as their accommodation would allow, but it must not be forgotten that they gave up many of their largest buildings at the change-over in 1948. After discussion with the appropriate local authorities,

TABLE V—CHANGE IN TURNOVER OF PATIENTS

—	Admission-rate (patients over 60)						
	1949	1950	1951				1952
			1st quarter	2nd quarter	3rd quarter	4th quarter	Jan.
Active beds ..	120	..	234	..	..	..	254
Average mthly. admissions ..	23	40	61	71	79	94	132
Whole-time medical staff	2	2½	3	3½	5½	6	6

it was decided to transfer permanently all the sick cases from two joint-user institutions—Eastville and Ridgewood—to regional-board hospitals. All the sick in these two institutions were evacuated to hospital and the beds which they occupied handed over to the two local authorities. The Regional Hospital Board made a considerable financial saving on the exchange but unfortunately lost approximately 200 beds. It was considered an advantage, however, to have all the sick in hospitals under the direct administration of the board. The local authorities facilitated the exchange by temporarily relaxing their standards of admission to accommodate frail ambulants whom they might have rejected in other circumstances. They profited by the exchange which gave them additional accommodation for their residents and allowed them to dispense with nursing staff. Even more important, it allowed them to develop the old joint-user institutions into modern hostels for aged people.

By the end of 1951 considerable progress had been made in the classification and disposal of the old population. There remained a hard core of uncertified long-stay cases: 208 frail ambulants, 118 bedfast, and 34 others. They had been in hospital for varying periods, as follows:

Period of stay (yr.) ..	1–2	2–3	3–5	5–10	10–15	15–20	20–25	25–50
No. of patients ..	59	23	44	46	59	60	35	34

Meanwhile new admissions were being investigated, treated, and assessed from the geriatric point of view, the social aspect of the case receiving at least as much attention as the clinical. The clinical aspect, however, was not neglected, and consultants were appointed to the hospital, representing all the specialties. The establishment for medical staff was increased from the equivalent of two whole-time doctors to six; a physiotherapy department was opened with a senior physiotherapist and two assistants. A full-time almoner has recently been appointed. Table V illustrates the increasing turnover in the active hospital beds. The full use of these beds has necessitated an increase in medical staff, and this increase is shown in whole-time units. The total number of admissions has increased from 568 in 1949 to 1187 in 1951. The 1951 admissions, and their disposal, are analysed by age-groups of under and over 60 in table VI.

To obtain an idea of periods of stay it was necessary to follow up patients admitted before the treatment centre had reached its present stage of development. The 851 admissions for the twelve months June, 1950, to May, 1951, inclusive, were therefore analysed. They fell into the following age-groups:

Age in years ..	0–29	30–39	40–49	50–59	60–69	70–79	80–89	90
No. of patients ..	45	25	42	86	173	296	159	25

The younger patients were almost all psychotics admitted under section 20 of the Lunacy Act. We have followed the fate of each patient up to eight months from the date of admission (table VII). It will be noted that 63% of the deaths occurred in the first three months. The first wave of deaths, which occurred within seven days, was probably exaggerated by the influenza epidemic of January, 1951. It is also accounted for by the fact that we do not refuse the dying patients in circumstances of social emergency. We believe that one of the most humane services a geriatric hospital can offer is to take the burden of nursing the terminal stages of illness off the shoulders of hard-pressed relatives.

The first wave of discharges largely represents patients with acute infections who responded quickly to antibiotics; properly, perhaps, they should have been admitted to general hospitals. The plateau in the second and third months demonstrates the fact that elderly patients cannot be hurried through hospital: sometimes it is the patient, sometimes the relative, who needs a rest, and sometimes both. The steady trickle of discharges up to the end of the period of observation represents the success of prolonged therapy in cases of stroke, arthritis, and cardiac failure. The low figure of 12% remaining in hospital appears satisfactory, since in the British Medical Association report (1947) a 20% residuum was considered reasonable. However, the influenza epidemic and the high rate of transfer by certification make our figures not quite comparable.

TABLE VI—ADMISSIONS AND DISCHARGES, 1951

Age-group	Died	Remaining in hospital	Discharged					Total
			Certified under Lunacy Acts	Own care	Care of relative	To local-authority hostels	To other hospitals	
Over 60	328	207	103	33	163	60	28	922
Under 60	30	30	136	17	35	9	8	265
Total ..	358	237	239	50	198	69	36	1187

Our idea of a geriatric centre at the central hospital is gradually taking shape. On the clinical side we have a block of acute beds and a set of long-stay annexes. The size of the hospital permits, and indeed encourages, development along these lines. As a routine every new case is "screened" in an admission ward. The amount of investigation is determined partly by the complexity of the case and partly by the prognosis. Thus an old person with anæmia, dropsy, or chronic cough who is mentally alert and in fair physical condition will be

TABLE VII—RESULTS OVER 8 MONTHS IN 851 PATIENTS ADMITTED JUNE, 1950–MAY, 1951

—	Length of stay													
	24 hr.	Under 1 wk.	1–2 wks.	2–3 wks.	3–4 wks.	1–2 mos.	2–3 mos.	3–4 mos.	4–5 mos.	5–6 mos.	6–7 mos.	7–8 mos.	Over 8 mos.	Total
Died	32	33	24	22	25	42	26	27	16	16	11	20	30	324 (*38%*)
Discharged ..	8	29	22	14	14	50	45	25	15	18	10	15	15	280 (*33%*)
Certified	29	73	7	15	8	1	4	1	3	2	1	0	1	145 (*17%*)
Still in hospital ..														102 (*12%*)
Total	69	135	53	51	47	93	75	53	34	36	22	35	46	851 (*100%*)

subjected to detailed examinations or, if necessary, sent to a special hospital. On the other hand, a malignant case with secondaries will be spared useless investigation to find the primary growth.

The scope of treatment available at the centre does not include major surgical operations. Whether we should encourage the [illegible] surgery within the hospital is still [illegible]. It would certainly be an advantage to have the *fractured femur pinned* or the enlarged prostate removed or the hernia repaired on the spot. We feel, however, *that our business is primarily* with the unclassified, and that special departments have a way of growing in size and importance until they occupy all available beds. We note the repeated recommendation that the geriatric unit should be part of a general hospital. We should like to order our development at the centre in such a way that facilities for diagnosis and surgical treatment were available, but could never overshadow the primary function of the centre.

To summarise briefly:

1. The population of Stapleton Hospital has been classified, and good progress made with the disposal of persons who were not in need of skilled nursing and medical care.
2. The framework of a geriatric centre has been laid down, *and a geriatric unit with ancillary departments is well* established.
3. The admission-rate to Stapleton Hospital has increased threefold.
4. Although our reorganisation has resulted in a net loss of 315 beds, the numbers on the local waiting-lists for admission to chronic hospitals were no higher this winter than last.

Subsidiary Geriatric Centre

To avoid excessive centralisation it was later recommended that a smaller unit should be established at Weston-super-Mare to serve local needs. This was agreed, and 20 beds in the local isolation hospital were taken over for this purpose. The unit is under the immediate control of the local consultant physician and is closely associated with the local general hospital. This means that patients have access to modern diagnostic and therapeutic facilities.

A small peripheral hospital—Ilex Lodge, in Axbridge—about 12 miles away, is linked to the Weston-super-Mare Hospital under the same hospital management committee. It was originally intended that the peripheral hospital should take all the frail ambulants and irremediables from Weston-super-Mare, thus providing a "lesser circulation" in this area. This would release beds at the centre for the admission of new cases and make the area practically independent of Bristol. To some extent this has been accomplished, but there are many practical difficulties to be overcome before achieving complete success in a project of this kind.

Peripheral Hospitals

The development of the smaller hospitals has been slow and difficult. At first sight it appeared that the obvious function of these hospitals was to house the long-stay patients, thus releasing beds at the centre for cases requiring active therapy or detailed investigation. Such an integration has been accomplished in West Cornwall and has contributed much to the success of the geriatric scheme in that area. Since the B.M.A. scheme (1947) envisaged such a function for the peripheral hospitals, it is worth while recounting the difficulties we have met. These same difficulties are more likely to occur in the future, whenever such a scheme is tried.

1. There was a natural healthy resistance to centralisation by the local management committees, medical and nursing *staffs, and patients.*
2. There are geographical considerations. Thus patients have a real or imaginary right to be admitted to the local hospital. The elderly person should not be removed too far from his relatives. If he is kept in touch with them it is easier to discharge him from hospital, and there are financi and other difficulties in the way of visiting if he is taken t the centre.
3. The local workhouse had become an institution and on the appointed *day, a hospital.* The *staff,* even thoug they lacked essential equipment and were too few in numb to undertake investigation and treatment on modern line had got used to treating some acute and urgent cases of illnes especially in old people. The great majority of doctor and nurses prefer to handle cases of acute illness with reason able prospects of recovery. The long-term case is often heavy burden on the nursing staff and is nearly alway unpopular.
4. These hospitals are usually in the charge of the loca practitioner. For many reasons he would prefer to admi cases from the immediate vicinity.
5. A *one-purpose long-stay* annexe for irremediables i just not practicable in a country town: we have found i impossible to get a nursing staff to stay in such a place An annexe which would cater for irremediables and frai ambulants is desirable, but again we find it does not wo well because of the lack of incentive for nursing staff.
6. The peripheral hospitals can just manage a few fema dements without *gross disorders of behaviour.* They canno take male dements, because of the difficulty of getting m nurses or orderlies in small towns. It must be rememb that to secure continuity of nursing in a single case 4 ma nurses would be required—3 for shift-duty and 1 for holidays.

These, then, are the difficulties we have met, and they are all inherent in the B.M.A. plan. We have had to compromise and give up the idea of rigid centralisation. Each of the peripheral hospitals admits *some* acute local cases *and accepts some long-stay cases from the general* hospitals and Stapleton Hospital. In return Stapleton Hospital *accepts the* heavy *nursing* cases and those senile dements whom the smaller hospitals cannot cater for. The turnover in the peripheral hospitals varies, being highest in the comparatively well-staffed central hospitals and lowest in the outlying village hospitals.

It is difficult to foresee how these hospitals could be fitted into a rigid scheme. The present administrative structure makes them practically independent of the Regional Hospitals Board in the matter of admissions. If the management committees are against the idea of them functioning as long-stay annexes—and in this they will have the support of the local medical an nursing staffs—there is no machinery for enforci centralisation. Indeed, *any attempt* to do so would o cause resentment and friction. It is probably better t encourage them *to function as hospitals* with a limited sphere of action as they are doing at the moment. There is a small range of disease in old people which they can treat well if they are given some help. Thus, in one of the hospitals with two half-sessions by a physiotherapist every week, the local hemiplegics are well treated. Then the treatment of acute infection with antibiotics is well within their scope; and congestive cardiac failures needing low sodium intakes are treated on a rice diet. With improvisation when necessary and full use of local resources, they can do good work.

In this way each peripheral hospital will have a miniature geriatric unit and a set of long-stay annexes. *Under the B.M.A. plan they tend to become the dumping*-ground of the central unit. Rightly or wrongly, the staff are convinced that the central hospital would pick out the "interesting" cases and unload on the periphery those patients who constitute a heavy burden on the available nursing staffs. To dispel this notion we have made it a policy to accept their most troublesome senile dements at the centre, although *this tends* to block active beds. We have also accepted heavy nursing cases to ease the [illegible] are very temporary shortage of nursing staff. [illegible] local authorities. They the number we [illegible] their accommodation would allow, number of beds f[illegible]gotten that they gave up many

The burden of ho[illegible]gs at the change-over in 1948. is carrying at the [illegible] appropriate local authorities.

TABLE VIII—ANALYSIS OF 276 INCONTINENT CASES IN A TOTAL POPULATION OF 725

—	Urine		Fæces		Fæces and urine		Incontinent with bedsore	
	F	M	F	M	F	M	F	M
Always ..	148	30	108	22	96	22	13	7
Occasional ..	61	32	42	21				
Total ..	209	62	150	43	96	22	13	7

was compiled from a recent survey of 276 incontinent cases.

Discussion

In spite of the attention devoted to the aged sick in recent years, we still have no agreed practical scheme for them. We use temporary expedients to meet the recurring crises.

Bluestone (1949), working in New York, considers that the hospital should continue to look after the old person in his home. Extramural geriatrics on this basis would not, however, be practicable here. Our medical organisation differs radically from that seen in the United States, and we doubt if our existing schemes of aftercare for the tuberculous or for sick children would be suitable models. The weight of numbers and the diversity of clinical problems in so large an aged population would be too heavy for any single hospital organisation to cope with.

Thomson (1949), after investigating conditions in Birmingham hospitals and institutions for the aged sick, concluded that they could be cared for within the existing framework of our medical organisation. His colleagues, Lowe and McKeown (1949), have made specific suggestions for disposing of the present population of the chronic-sick hospital. They think one-fifth might go to the general hospitals, one-fifth to long-stay psychiatric annexes, and three-fifths to homes or hostels. Even if the general hospitals accepted their quota, thereby blocking beds which serve the needs of the productive age-groups, we still consider the scheme unworkable. The classification of the senile dements appears too rigid. We know the local authorities are short of accommodation, and the able-bodied elderly destitutes outside have first call on their resources. It seems unlikely, therefore, that they will accept the remaining three-fifths, which presumably includes the senile infirm, unless directed to do so by new legislation.

The third view which merits consideration is that embodied in the B.M.A. plan (1947). This plan was designed to prevent dumping of old people—sick and well, sane and dement—together in buildings which were inadequate from every point of view. It is centred on the geriatric unit which has the dual function of investigation and treatment. Investigation includes classification. We believe the geriatric unit has come to stay, for there is no doubt that more can be done for the treatment of disease in old people than is apparent from reading current textbooks of medicine. Like other workers in geriatric units, we have achieved an occasional miracle of rehabilitation in mobilising the hemiplegic and sending the bedfast (one of whom had been in bed for nine years) back to gainful employment. But the melancholy fact remains that only a fraction of the aged sick can be rehabilitated to this extent. We would emphasise this, because there is a widespread belief th[illegible] fficient physiotherapy were available [illegible] be solved. [illegible] for the disposal [illegible] further treatment. [illegible] to remain, the crux [illegible] on is, in our opinion, just as likely to re-create the problem which the plan was designed to solve: the practical difficulty lies in ensuring that the annexe itself does not become a dump.

	S		
Certified	29	73	
Still in hospital ..			
Total	69	135	53

For that reason, as we have explained, we have cheerfully accepted a compromise. Like the central hospital, the peripheral hospitals will carry their share of long-stay cases; but they will not be annexes or dumps of the central hospital. In this way we hope to avoid the worst features of centralisation and prevent the development of dumps. We believe that the most that can be done is to guide the evolution of the peripheral hospitals towards higher standards in the diagnosis and treatment of the aged sick.

The frail-ambulant group presents a thorny problem, demanding more attention than it has yet received. Sheldon (1948) found that 7·7% of old people are a strain on their relatives. The frail ambulant, then, is part of a large social group of senile infirm whose dimensions we can only guess at. It is certainly far too large for the hospital accommodation we possess. Fortunately relatives are willing and eager to keep the majority at home, but this solution cannot be pushed too far. In weighing the burden of hospital or institutional care it must be remembered that many cases—especially the mentally infirm—require whole-time attention. This may mean that one adult per aged person is kept away from productive work—a serious loss in an industrial community. In a hostel or home for such persons a ratio of 3 or 4 cases to 1 staff functions quite well. While, therefore, we advocate home care as a general rule, we recognise that institutional care may be more economical in many cases. What form this institutional care might take should be the subject of experiment. A "mixed institution" in which there is ready access to a hospital bed provides a good solution in theory. From our experience of "joint-user" institutions we do not consider that these provide the answer.

We are only beginning to tackle the problem of the waiting-list. At this stage of our experience, and mindful of what has been reported from other areas, we still regard this as part of the great problem of the senile infirm. It is not enough for a hospital admissions officer to report that the waiting-list has been cleared of emergencies. Sheldon's 7·7% are a reservoir which no hospital system can drain.

We are beginning to understand what the future scope of our work is likely to be. The general practitioner, who in the long run must be the arbiter of our functions, is already sending us most of his cases of stroke. Inoperable cases of malignant disease come in partly from the general practitioner and partly from other hospitals. Otherwise an amorphous mass of senile infirmity and unclassified illness comes into our wards for classification, treatment, and disposal. We find ourselves drifting away from the idea of a small intensive geriatric unit which is part of a general hospital. The large hospital gives us long-stay annexes on the spot. In the small unit a rapid turnover in beds might well become the most important consideration, and this should never be so in geriatrics: response to treatment is often slow and the social problems of an elderly patient cannot always be solved overnight. Our present line of development keeps us in close touch with the long-stay annexes and at the same time gives the peripheral hospitals a share in the active treatment of remediable illness.

Summary

The integration of the chronic-sick hospitals in the Bristol clinical area to provide a geriatric hospital service is described.

The organisation is based on a geriatric centre in a large city hospital to which the peripheral hospitals

are linked. The latter do not function as long-stay annexes of the centre.

The difficulties inherent in any scheme involving rigid classification and centralisation are described as they have been encountered. Some popular solutions of the hospital problems of the aged sick are analysed in the light of our experience.

We have pleasure in acknowledging the help and encouragement of the South Western Regional Hospitals Board and the hospital management committees in the Bristol clinical area. In particular we should like to thank Dr. S. Datta, senior medical officer, and Mrs. D. Pearson, matron of Stapleton Hospital.

REFERENCES

Amulree, Lord (1951) Adding Life to Years. London.
Bluestone, E. M. (1949) *J. Gerontology*, 4, 305.
British Medical Association (1947) Care and Treatment of the Elderly and Infirm. London.
Brooke, E. B. (1949) *Lancet*, i, 462.
Cosin, L. (1948) *Proc. R. Soc. Med.* 41, 333.
Lowe, C. R., McKeown, T. (1949) *Brit. J. soc. Med.* 3, 10.
Royal Commission on Population Report (1949) H.M. Stationery Office.
Sheldon, J. H. (1948) The Social Medicine of Old Age. London.
Thomson, A. P. (1949) *Brit. med. J.* ii, 243.
Warren, M. W. (1943) *Ibid*, ii, 822.
— (1948) *Proc. R. Soc. Med.* 41, 337.
Wilson, T. S. (1952) personal communication.

ITALIAN HOSPITALS

The European Tradition

FROM A CORRESPONDENT

THE words *Lavori in Corso*—"work in progress"—greet the visitor to Italy on every hand. The country is, by contrast with Great Britain, an architect's paradise, and, especially where there has been much destruction during the war, cream and apricot tinted blocks of flats are being busily erected. Italy today is rapidly recovering much of its old attraction for visitors from Britain; her native friendliness and her proud heritage of the Renaissance are reasserting in the European scale of values a place well recognised in the 19th century but almost lost to sight under the long dominance of the Triple Alliance and of Fascism.

DIFFERENT VALUES

Some thirty representatives from Great Britain have just participated in a study tour organised by the International Hospital Federation on the invitation of the Italian Hospital Federation. The tour, which was the second in a post-war series of alternating congresses and study tours, covered in a fortnight the principal hospitals in and near Milan, Bologna, Florence, Rome, and Genoa. Most of the participants hailing from Britain (and other northern climes) had to confess that they had been reprehensibly unconscious either of the magnitude of the tradition of the greater hospitals in Italy or of the remarkable series of specialist centres developed and financed out of the funds of the industrial insurance organisations there. With us, knowledge of the European hospital tradition too often stops short at a vague recollection that Salerno preserved something of the tradition of Greek medicine, and that Italy later laid the anatomical foundations of our modern medicine. It was, therefore, a memorable experience to enjoy privileged visits to hospitals of the great centres of Northern Italy; and, above all perhaps, to the Arcispedale di Santo Spirito in Rome where there are still in use the immense wards built during the Renaissance.

Here the visitor could stand in the ancient library, and through an opening in the wall gaze down on the 50 or 60 beds ranged far below, among which moved the white figures of the nuns and their assistants. The magnificence of the architecture, the painted wooden ceiling, the great height of the ward—sufficient to take some four modern wards superimposed one above the other—and the peacefulness of the scene offer the visitor a vivid glimpse of the days before the study of medicine began to be conducted at the bedside, and of a hospital where the sick are still cared for in restful surroundings.

It was from hospitals such as this, and the famous Ospedale Maggiore at Milan (where the beautiful old buildings suffered from Allied bombs) that the men who set about rebuilding St. Bartholomew's and St. Thomas's about the end of the 17th century must have drawn much of their inspiration. To set foot in such hospitals is to regain perspective.

Conservatism in hospitals is a neutral thing; it may obstinately maintain practices out of keeping with the social structure of the period, or it may on the other hand preserve a sense of proportion and a scale of values through periods of change and materialist outlook. Close and careful comparison between hospital practices in the best Italian tradition and, let us say, that of the English-speaking countries might show that, in some directions at all events, the advantage rests with the older tradition. In Italy, for example, the impact of the Nightingale and post-Nightingale approach to nursing has been much less than in Great Britain and in America and there are to be found schools of nursing, such as that at the great Careggi Hospital at Florence, where the cultural background plays its part in a way not often, if ever, found in our own schools. Is there some danger that in a world where technical qualifications and [illegible] to be held in ever higher regard, and [illegible] prestige in international affairs, the simpler prodedures—and may one add comparative freedom from centralised control—of the Italian schools will be too lightly set aside? The use of historic buildings, such as the old 14th-century Villa Peppi, for the housing of student nurses may not square with the standards we like to lay down; but it may help to preserve values we are in danger of losing.

PROVISION AND UPKEEP

Italy has developed a complex system of industrial insurance to supplement the older and still essentially voluntary hospital system of the cities. The visitors were shown with justifiable pride a number of examples of buildings of the '20s and '30s where the facilities could challenge comparison with any in the world. Of this development perhaps the most striking example was at Sondalo, where an astonishing group of solidly constructed many-storey blocks for the treatment of tuberculosis are perched high up on the mountain-side at the head of the valley where Como lies far below. How it is possible to keep within limits the maintenance cost of so isolated a community was puzzling enough, but apparently the problem has been solved. Here were vistas of snowcapped mountains and the bracing air of the nearby Engadine, coupled with engineering feats that defy description. The central supply of food to the various blocks is achieved by a system of cables and pulleys up and down the mountain side. This and other examples of specialised provision of modern units for cases drawn from all over Italy, and paid for partly by the insurance societies and partly from the public funds for the indigent, bear witness to the vigorous power of adaptation to circumstances inherent in the system. Discussing its merits with visitors from Britain, the Italians show themselves alive to the need in Italy for a measure of "regionalisation," as recommended by the World Health Organisation commission on the Italian Health Service which published its findings in 1949, and equally to the danger of rigid adherence to any system of finance out of public funds, and to the value of a device which, like the use of the industrial insurance funds, enables the hospital system to be harnessed to ndustrial activity and capable of moving in some sense in step with it.

Something of the same thought is traceable in the attitude of the voluntary donor in Italy—a belief that the important thing is the gift for capital, and that if this is provided means will somehow or other be found to keep the institution alive. The excellent children's hospital at Genoa, founded not so long ago by Count Gerolamo-Gaslini in memory of his daughter Giannina, is an example of the provision of a great hospital by a single donor; he specifically said that he had preserved no money for its maintenance, "knowing too well how the well-being of charitable institutions based on patrimonial revenues, in these times of selfishness and changes in monetary values, becomes prejudiced." This hospital is by no means the only example in Italy of major development created by voluntary effort within recent times.

COMPARISONS

The stir and pulse of life was evident in all that the visitors were shown. In the opinion of the World Health Organisation report, the level of the health services in Italy is, generally speaking, high. The historical circumstance of the development of the hospitals of Italy, as of our own, out of a proud voluntary heritage, supplemented in both cases though in different ways out of public monies, offers an opportunity to compare notes and to measure how far the rationalisation which we have assuredly been able to achieve may yet have to be paid for by some loss of flexibility.

The visit of the International Hospital Federation to Italy was warmly welcomed by the Italians and certainly held out a promise that closer comparison of many aspects of hospital work would prove both practicable and illuminating.

LABELS FOR GASSING CASUALTIES

THE practice of labelling casualties is familar to those doctors who have served in the Armed Forces, where it has proved a useful method of conveying information about treatment given in the forward areas. Hitherto it has not been adopted systematically in peace-time casualty work, though workers in tunnels and compressed-air chambers are given labels to wear against the contingency of an attack of compressed-air illness coming on after leaving work.

The Association of British Chemical Manufacturers has issued a book of labels [1] recommended for use when a gassing casualty is sent to hospital. The labels indicate clearly the type of gas to which the patient has been exposed; the time and severity of exposure; the signs and symptoms of poisoning; the first-aid treatment already given; and a suggested scheme for immediate and subsequent medical treatment. For some time the works safety committee of the association had felt that an important contribution to industrial safety would be made if hospitals could have a correct history and diagnosis of cases sent from chemical works, in order that the appropriate treatment might be instituted without delay. They say that the comparative rarity of the cases and the variety of gases have resulted in delay in exact diagnosis and therefore in the selection of appropriate treatment. Again, some types of gassing need specialised treatment, details of which are not readily available to the hospital doctor.

The booklet contains 19 separate labels (A–S) dealing with 50 different gases.

Label A, for instance, is concerned with six irritant gases (acetic anhydride, ammonia, chlorine, formaldehyde, hydrochloric acid, and sulphur dioxide) for which the first-aid and hospital treatments are similar. Label E deals with nickel carbonyl, nitrous fumes, phosgene, and phosphorus oxychloride, all of which are classified as dangerous gases. Label G is devoted to 12 narcotic gases, some of which are acetylene, methyl chloride, and trichlorethylene. Those gases for which a special label is required include hydrogen cyanide, bromine, arsine, carbon disulphide, and hydrogen sulphide. Fluorine and hydrofluoric acid, classified as extremely irritant gases, are dealt with on label C. This label gives not only the signs and symptoms of gassing, the first-aid treatment, and the immediate and subsequent medical treatment, but also the appropriate treatment for burns of the skin and eyes.

It was thought that possibly use of the labels might arouse opposition among the hospital medical staffs, but it is difficult to understand why a busy casualty officer should object to having a suggested line of treatment indicated to him. Most of them will welcome the labels, because there will be no need to refer hurriedly to a textbook of toxicology, which, if it is out of date, may not even mention the gas which caused the casualty. The medical panel of the association suggests, however, that where there is a medical officer in a factory, he should get into touch with the hospital authorities and explain the reasons for introducing the labels. The Factory Department and its medical branch support the scheme; and the aid of the British Medical Association, the Association of Industrial Medical Officers, and the regional hospital boards has also been invited.

ANALYSIS OF HOSPITAL ACCOUNTS

THE first detailed costing returns for hospitals in the National Health Service in England and Wales [1] have been published by the Ministry of Health. They are for the year ended March 31, 1951, and cover some 2750 hospitals.

Early in 1950 the Minister of Health, on the advice of the Central Health Services Council, invited King Edward's Hospital Fund for London and the Nuffield Provincial Hospitals Trust to undertake a complete unit costing of a small number of representative hospitals. The ultimate form of costing will be considered in the light of their report. As an interim measure a relatively simple system of cost analysis, based on the headings of the financial accounts, has been introduced and forms the basis of the present returns. This system was recommended in a report by a committee appointed by the treasurers of regional hospital boards.

Every hospital is classified in the return according to its primary function—for example, wholly general,

AVERAGE COST PER WEEK OF MAINTAINING A PATIENT IN THE YEAR ENDED MARCH 31, 1951

Region	Wholly general			Mainly chronic			Maternity			Mental			Tuberculosis		
	£	s.	d.	£	s.	d.	£	s.	d.	£	s.	d.	£	s.	d.
Newcastle upon Tyne	12	6	6	6	17	1	15	9	8	3	11	11	6	14	7
Leeds	13	4	7	7	13	1	16	19	0	3	9	10	9	0	9
Sheffield	12	11	1	5	18	8	15	4	1	3	18	1	7	10	6
East Anglian ..	13	14	11	6	17	1	15	4	4	3	10	6	9	15	0
North-West Metropolitan	17	0	8	11	3	1	17	14	7	4	5	2	12	10	11
North-East Metropolitan	14	7	11	7	13	11	19	0	7	4	2	3	9	16	1
South-East Metropolitan	14	14	11	11	17	2	17	10	6	3	13	1	10	7	4
South-West Metropolitan	14	1	4	7	16	0	15	15	4	4	2	10	8	18	11
Oxford	16	1	7	6	10	0	17	14	0	3	17	0	10	14	4
South Western ..	15	1	2	4	11	9	15	11	9	3	15	7	9	7	7
Welsh	11	18	6	7	12	10	16	5	3	4	0	6	8	2	8
Birmingham ..	13	0	0	9	0	0	18	4	7	3	9	6	8	2	6
Manchester ..	11	19	0	5	7	3	14	5	2	3	7	6	7	8	0
Liverpool ..	11	10	3		Nil		14	1	4	3	7	10	8	9	1
National averages	13	10	3	6	18	4	16	9	5	3	15	11	8	17	2

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[1] A System of Labels for Gassing Casualties Sent to Hospital. Association of British Chemical Manufacturers, 166 Piccadilly, London, W.1. 3s.; 1 doz. labels 2s.

[1] National Health Service: Hospital Costing Returns, year ended March 31, 1951. H.M. Stationery Office. 10s.

mainly chronic, maternity, or mental. Three main sets of figures are worked out: (1) the total inclusive net cost per week of maintaining a patient; (2) the same cost after allowing for outpatient expenditure (this is done by assuming that five outpatient attendances equal, for costing purposes, one inpatient day), and (3) the same cost further adjusted to allow for "vacant-bed factor" (beds staffed but not occupied).

For the purpose of comparing the cost per patient between hospitals of the same type or between one type and another, it is considered that the inclusive net cost after allowing for outpatient expenditure (where applicable) provides a reasonable basis for comparison. In the accompanying table this figure is used to compare the average cost per patient in various types of non-teaching hospitals in the fourteen hospital regions of England and Wales together with national averages. For teaching hospitals classified as wholly general the average weekly cost per inpatient, computed on the same basis, was £23 16*s*. 10*d*. in London and £17 5*s*. 10*d*. in the provinces.

Mr. Iain Macleod, the Minister of Health, has told hospital authorities that the primary object of these costing returns is to enable them to make comparisons between the costs of comparable individual hospitals and between those costs and the regional and national average figures where these have been provided. He adds: "Investigation of the causes of the differences thrown up should be of value in securing economy and improving efficiency in administration, and regional hospital boards, hospital management committees, and boards of governors are asked to make the fullest possible use of the figures."

HEADQUARTERS STAFF OF REGIONAL BOARDS

The Medical Whitley Council (Committee "B") have reached the following agreement on the salary scales for assistant senior medical officers and medical officers on the headquarters staff of regional hospital boards. The Minister of Health has approved the new scale, which is to be retrospective to Oct. 1, 1950.

Assistant senior medical officers in all regions of England and Wales, and in the Western and South Eastern Regions of Scotland: £1500 × £75(4) × £100(1)–£1900 per annum.

Assistant senior medical officers in the Eastern, North Eastern and Northern Regions of Scotland: £1500 × £75–£1800 per annum.

Medical officers in all regions: £1250 (at age 33 or over) × £50–£1500 per annum.

Officers in the Metropolitan Police Area will receive a London weighting allowance of £50 per annum.

Public Health

Notifiable Diseases

THE division of epidemiological services of the World Health Organisation has now prepared the second part of its Annual Epidemiological and Vital Statistics, 1939–46.[1] The first part, devoted to population and vital statistics, appeared last year. The latest volume deals with notifiable diseases, and contains the figures reported by more than 150 States and territories. Whenever possible both the number of cases and the deaths from each of 19 diseases are given for every month of the eight years. Annual figures are tabulated for another 12 diseases. Clearly and painstakingly compiled, this publication represents the only official source of information covering so large a part of the world's population. It continues the sequence of Annual Epidemiological Reports issued from 1923 to 1938 by the League of Nations.

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[1] Annual Epidemiological and Vital Statistics, 1939–46., Part 2. Cases of and Deaths from Notifiable Diseases. W.H.O. Geneva. 1952. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1. Pp. 202. £1.

In England Now

A Running Commentary by Peripatetic Correspondents

FOR some time we have dabbled in embryology to the extent of drawing red blue and yellow diagrams on a blackboard before the assembled multitude, and to us Experimental Embryologists have acquired the status of mythical Culture Heroes. It was therefore disturbing to meet one in the flesh and to discover that he is besieged by misgivings like other men. From his discourse we gathered that chromosome—
since triploid rabbits and haploid mice
able from normal ones. Haploid newts, we noted with satisfaction, are sterile. We learnt that the insertion of a piece of bootlace will induce differentiation of the neural ectoderm, and our eyes became glassy at the mention of mosaics, cytoplasmic gradients, and grey crescents.

That a man who habitually scrambles the contents of a sea-urchin's egg with ultrasonic waves, and who o[illegible] divided the nucleus of an embryonic axolotl with a thin snare should ever be in doubt seems to us incredib[illegible] But so it is: under the thin crust of our red blue [illegible] yellow diagrams lies a seething morass of uncertain[illegible] We are buying some green chalk tomorrow.

* * *

It is a big step forward for the young medical author (and a welcome one for his editors) when he appreciates the niceties of bibliographical abbreviation as laid down in the *World List of Scientific Periodicals.* This will show him how to avoid such bêtises as *B.M.J.* and *J.A.M.A.* and works of supererogation such as *J. Pharmacol. & exp. Ther.* or *Proc. Staff Meet. Mayo Clin.* After a couple of days with the World List at his elbow he will be clearing such hurdles as *J. Lab. clin. Med.* and *Proc. Soc. exp. Biol., N.Y.*, with never a stop or capital misplaced or a superfluous syllable. He will enjoy the very special thrill of pruning oversize titles like *Bollettino della Malattie dell' Orecchio, della Gola, della Naso, di Tracheo-Bronco-Esofagoscopia e di Fonetica* to the laconic *Bol. Mal. Orecch.*

Foreign publishers are apt to follow a code of abbreviations of their own, and this morning, when running through a Belgian abstract journal, we were shaken to find a paper on the ætiology of peptic ulcer credited to *Wikliwo*, **62**, 674, 1950. This raffish-looking title suggested one of those glossy Continental weeklies, filled with risqué cartoons, which one finds in the better Harley Street waiting-rooms. With bitter memories of instigating library searches for the current volume of *Ibid*, we appealed to a learned colleague, schooled in military terminology, who identified it in a few seconds as the journal known in our chaster code as *Wien. klin. Wschr.* NATO, SHAEF, NATSOPA; ROSPA, and now WIKLIWO; only a little farther down the slippery slope and we shall find ourself figuring as a case-history in the *J. ment. Sci.* (or will it be JOMESCI?).

* * *

Our new projector arrived the other day, in a couple of imposing packing-cases, and we all assembled eagerly on the chance of being allowed to play with it. The *Instruction and Service Manual* began in a restrained motherly key:

> "Unscrew the lid of the large case and lift out the cabinet, taking care not to scratch the finish . . . clean out the inside of the cabinet and dust the screen carefully . . . gently lift it from the case and remove the cross batten . . . make sure you have thoroughly washed behind the ears."

For the next two pages all was sweetness and light; a paragraph was devoted to the discovery of the main switch A, and another to the identification of the earth wire marked *Earth*. A fleeting chill ran down our spines over two sinister nuts T1 and T2 which had to be exactly $7\frac{29}{32}$ in. (19·97 cm.) apart; but otherwise the gentle flow of Instruction soothed and relaxed us. It was just like 'Meccano.'

This could not last, and by the fourth page a peevish admonitory note had crept in: "Ensure that the shutter operating pin P, if removed, is replaced square end up." This began the rot. Search as we might, we could discover no trace of the shutter-operating pin P, or indeed of its square end. We could locate the coupling screw K, the counter-balance arm R, the operating cams and slide claw, and for that matter the locking nut Y and the spring and collar Q. But no shutter-operating pin P.

At this point we discovered that the milled knobs G looked vaguely unfamiliar, and that there was no sign of the hand-control knob E or the pair of knurled screws H. We are scientists—men trained to assess evidence. A glance at fig. 7 confirmed that we had spent an hour assembling one type of instrument with the manual intended for another. Our professor is even more scientific; when the matter was brought before him, it took him only half an hour to discover that he had ordered and received an instrument not designed for projecting at all.

* * *

Your correspondent (June 14) need not, after all, cross to Eire in his hunt for bats. The other evening a friend and I were trying to pull out the trout that are said to lurk in the River Tees. We had no luck, even though my friend was using a rod that looked like something between a large pole and a clothes-prop. Then came dusk, and with it innumerable bats. As we made our last few despairing casts, we noticed that they were all around, and especially round the flies on our lines. It was no time before the first bat was hooked. Unfortunately this method does not seem to be patentable; but if your correspondent gets in touch with us, he will find that our terms compare favourably with those of other frustrated anglers.

* * *

Most anatomists eke out a meagre livelihood by distilling the essence of their subject to improbable groups of people, and in common with many of my fellows I teach anatomy to art students. For some time the class and I have felt that all was not well. Now at last I have put my finger on the reason—this purely representational stuff is getting us nowhere. Next year I am to start a course in Commercial Anatomy for Fashion Illustrators, thus at one stroke raising myself above the ruck into the realms of a possible distinction award and offering to my class the chance of eventually earning a living.

The course will concentrate on fundamentals: we shall start with the Evidences of Structural Adaptation to Haute Couture. Under this heading we shall deal with the Atretic Waist, the Pinhole Nostril, the Double-jointed Digit, and the High Centre of Gravity. We shall pass to the Relationships Between Bodily Proportions and Artistic Media. In this section comes the discussion on the correlation of relative head length with the glossiness of the paper expressed in reflectivity units, and the account of the Expanding or Telescopic Thigh, with notes on the peak values for thigh length obtained in half-tone blocks advertising 'Nylons.' There will be a lecture on o.s. illustrating, with a word on the Bosom, and some remarks on the Undistributed Middle. The course will end with a discussion on Commercial Postural Equilibrium, with a subsection dealing with the use of the Shooting Stick.

Entries are already being received: *make sure of your booking NOW*.

* * *

Does this scrap of conversation, overheard in an Aberdeen theatre, illustrate the Scottish attitude to education?

Aunt.—How are you getting on at school?

Child.—Oh, very well.

Aunt.—What's your best subject?

Child.—English. I was first in my class—or rather bracketed first with another girl; I couldn't be better than that.

Aunt.—Oh yes you could. You might have been first by yourself!

* * *

News from the Clinic.—Mother with supremely healthy infant: "Baby's that wheezy, doctor. Grandma's rheumatics is bad too. Now if I could have a certificate for coal . . ." Next week outraged mother pointing to two minute and undiagnosable spots on baby's cheek: "Just look at 'is face, doctor. All over burns 'e is! That awful coal you gave me—it spitted!"

Letters to the Editor

THE McNAUGHTEN RULES AGAIN

SIR,—The recent case of Reg. *v.* Windle[1] is of such importance and interest, in both its medical and its legal implications, that we should like to emphasise some aspects not fully dealt with in your report.

It is a matter for regret that the case did not go to the House of Lords. Deciding the criminal responsibility of mentally deranged persons frequently involves the application of psychiatric ideas current in the second half of the 20th century to a set of rules formulated in the first half of the 19th. This is no easy task. So long as it has to be attempted, no opportunity should be lost of obtaining the assistance of the highest appellate tribunal in the further elucidation of the problems of interpretation set by the wording of the McNaughten rules.

Windle was charged with the murder of his wife by administering to her aspirin tablets with the intent to kill her. The evidence adduced by the prosecution showed that Windle had given his wife one hundred tablets in a cup of water. This she had contrived to take. The facts proved by the prosecution were not disputed; the sole defence was insanity.

The evidence of the psychiatrist called by the defence (the undersigned H. E. H.) indicated that the accused was a man of low intelligence, the spoilt youngest of a large family, who some four years previously had married a woman eighteen years his senior. This woman was domineering in character, and in the first two years of the marriage manifested behaviour disorders of an aggressive type. During the last two years of her life, however, her behaviour changed into that of a psychotic depressive, progressively deteriorating, and showing typical suicidal tendencies. Her husband nevertheless remained, throughout this latter period, completely under her influence and entirely submissive to her will. She suggested to him that she should die and that he should be instrumental in bringing about her death. This suggestion he was powerless to resist. In the psychiatrist's opinion, the accused, at the time he mixed the tablets and gave the mixture to his wife, knew what he was doing and knew that it was contrary to law, but he did not know that what he was doing was morally wrong. His inability to perceive the moral wrongness of his act (in other words his "defect of reason") was due to his being so completely under the influence of his wife that his capacity to think and act independently of her was paralysed. In these circumstances his "disease of the mind" was regarded as "communicated insanity." On this view the case provides as clear an illustration as one could have of a state of mind in which a person is conscious that what he is doing is contrary to law, but at the same time does not know that it is morally wrong.

This diagnosis was, with some reservation, concurred in by the prison medical officer called in rebuttal by the prosecution. This assessment of the state of mind of the accused is by no means the equivalent of saying that he thought that what he was doing was "a kindly act" or "beneficial" or "justified," though the Court of Criminal Appeal appear to have assumed that it is.

At the trial, the judge ruled that there was no evidence of insanity to go to the jury. The Court of Criminal Appeal held that the judge was entitled to withdraw the issue of insanity from the jury. The Lord Chief Justice, delivering the judgment of the Court of Criminal Appeal, said: "A man might be suffering from a defect of reason, but if he knew that what he was doing was wrong, by which was meant wrong in law, he was responsible."

If one looks at the original answers of the judges to the questions addressed to them by the House of Lords—the McNaughten rules—one finds, in connection with their explanation of the meaning of the rule with which we are now concerned, these words: "if the accused was conscious that the act was one which he ought not to do, and if that act was at the same time contrary to the law of the land, he is punishable."[2] The decision in Windle's case has the effect of reducing this to: "if the accused was conscious that the act was contrary to the law of the land, he is punishable."

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[1] *Times*, May 13, 1952; (1952) 2 A.E.R.1; see *Lancet*, May 24, 1952, p. 1064.

Support for this narrower interpretation is obtained from the decision of the Court of Criminal Appeal in the case of Codere.[3] The judgment of the court in that case contains these words:

> "The question of the distinction between morally and legally wrong opens wide doors. In a case of this kind, namely, killing, it does not seem debatable that the appellant could have thought that the act was not morally wrong, judged by the ordinary standards, when the act is punishable by law, and is known by him to be punishable by law. It was suggested at one time in the course of the argument that the question should be judged by the standard of the accused, but it is obvious that this proposition is wholly untenable, and would tend to excuse crimes without number, and to weaken the law to an alarming degree . . . once it is clear that the appellant knew that the act was wrong in law, then he was doing an act which he was conscious he ought not to do, and as it was against the law, it was punishable by law."

One sees in these sentences not only the faulty logic on which the argument is based, but also the fears which induced it. If an act is contrary to law, men who judge by the ordinary standards (i.e., reasonable men) know it is an act they ought not to do. If one applies these standards to the accused (i.e., if one assumes that he is a reasonable man) it follows that if he knows that an act is contrary to law, he, too, must know that the act is one he ought not to do. Therefore he is responsible in law. In other words, in order to determine whether or not a man is insane, so as not to be responsible in law for his acts, one assumes that he is a reasonable man.

We, therefore, go further than you did in saying that the dictum—it is more than dictum, it is *ratio decidendi*—of the Lord Chief Justice in Reg. *v.* Windle might in other legal contexts be open to argument. We suggest that it involves a misinterpretation of the McNaughten rules, is based on illogical reasoning, and ought to be overruled by the House of Lords.

The late Lord Atkin, in an address to the Medico-Legal Society in 1925,[4] said that the application of the law relating to insanity "is very much more generally liberal than would be the case if it were carried out in strict accordance with the letter."

Windle's case would seem to indicate that whatever liberality juries may still display when given the opportunity, the judicial tendency is in the opposite direction and that the application of the law is now less liberal than would be the case if it were carried out in strict accordance with the letter of the McNaughten rules as originally laid down.

H. E. HAAS
D. R. ELLISON.

Birmingham.

HALLUX VALGUS

SIR,—Everyone interested in the development of hallux valgus will be grateful for the article last week by Dr. Hardy and Mr. Clapham. This effectively disposes of the idea that the wide spacing of the first intermetatarsal space might be the cause of hallux valgus and enables us to concentrate on the years when the condition is obviously developing—namely, the period of school attendance. Whilst Dr. Hardy is not prepared to condemn footwear as the culprit without further evidence, and suggests that some investigation should be made among barefoot peoples, there is good reason to assume that footwear, which we know is most unsatisfactory among school-children, is playing an extremely significant part in this condition.

Personally, I have been anxious that some survey should be made among barefoot peoples, and I would suggest that the World Health Organisation might include this among their research projects. They will find that few parts of the world are now outside the range of the modern shoe, and it may be difficult for them to find an area with a suitable group which can be statistically analysed. The true facts should, however, be established so that we may build up a plan of preventive action.

Ealing, London.

W. G. BOOTH
Medical Officer of Health.

RE-GROWTH OF HAIR IN PREGNANCY

SIR,—In view of Dr. R. A. Wilson's article of March 29 (p. 646) on the effect of A.C.T.H. on hair-growth in alopecia areata and alopecia universalis, the following case be of interest.

A woman, aged 31, was referred to the Endocrine Department for total alopecia. She first lost her hair at the age of 15; the hair grew again after three months' treatment with ultraviolet irradiation. Her second attack was at the age of 18, after the death of her father; this time the hair grew again spontaneously. She was married at 21. A year later the alopecia recurred, and it then alternately improved and relapsed until she was 26, when her head became completely bald. The condition was resistant to all the usual forms of treatment. At 28 she became pregnant, and her hair began to grow again, reaching a length of about 3 inches. Three months after her confinement, however, all her hair fell out again within a fortnight; she fed her child at the breast for nine months. She became pregnant again at 31, when her hair began to grow almost immediately.

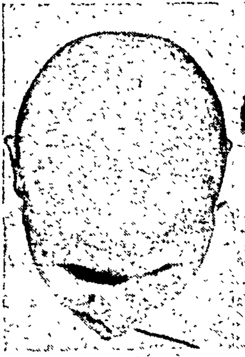
Fig. 1

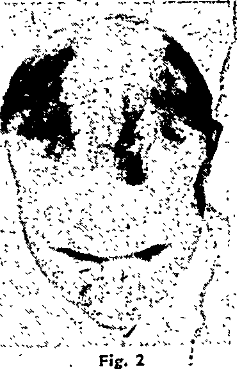
Fig. 2

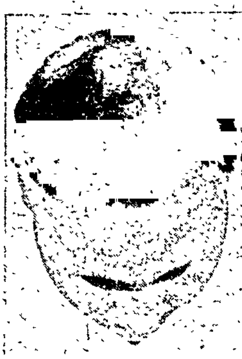
Fig. 3

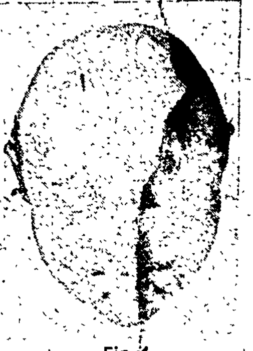
Fig. 4

The condition of her head hair when we first saw her, on July 17, 1951, is shown in fig. 1, when she was four months pregnant. Four months later (fig. 2) there was a considerable re-growth of head hair. Ten weeks after her confinement (fig. 3) she had still more hair on her head, though she said it was beginning to fall out again. Since then she has continued to feed her baby at the breast, but her hair has steadily fallen out (fig. 4).

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[2] See Reports of State Trials, N.S. vol. 4, p. 931; and 10 Cl. & F., 210.
[3] 12 C.A.R., p. 21.
[4] *Law Times J.* 159, 436.

Waisman and Kepler[1] reported six cases of alopecia areata in which there was a substantial re-growth of hair in one or more pregnancies, and the hair began to fall shortly after parturition. On the other hand, two other patients of theirs developed alopecia for the first time during pregnancy and a further two did so in their puerperium. Walker and Rothman[2] reported three cases of alopecia areata, two of them leading to alopecia universalis, in which there was complete re-growth of hair during pregnancy. In the first case there was a total relapse twelve days after delivery; in the second the hair remained until lactation ceased, eight months after the confinement; and in the third the hair stopped growing after delivery and fell out suddenly two years later.

It was the improvement of rheumatoid arthritis during pregnancy that led Hench and his colleagues to discover the beneficial effects of cortisone in this condition. Dr. Wilson's report on the effect of A.C.T.H. in alopecia universalis, and that of Dillaha and Rothman,[3] recording re-growth of hair in three out of four cases of alopecia universalis during treatment with cortisone, suggest that there is a parallel between alopecia areata et universalis and rheumatoid arthritis, both conditions improving during pregnancy or under treatment with cortisone or A.C.T.H. In both conditions the improvement in pregnancy is apparently due to the physiological increase in the secretion of 11-oxysteroids by the adrenal cortex; and presumably this mechanism is reproduced by the administration of A.C.T.H. or cortisone.

In Dr. Wilson's cases the effects of A.C.T.H. were only temporary. Dillaha and Rothman's report was a preliminary one, but hair-growth has continued for 4–7 weeks under the influence of cortisone by mouth. It is interesting to note that in all but one of their patients the hair of the head, the eyebrows and eyelashes, the beard, and the body-hair grew again during treatment, though in one case the pubic and axillary hair did not grow. Their only failure was in a man aged 21, in whom the onset of the condition was before puberty, at the age of 8. The dosage of cortisone was 150 mg. daily by mouth, and in one case this was gradually reduced to 25 mg. daily without *loss of effect.*

It seems that the use of cortisone or A.C.T.H. is worthy of further trial in alopecia areata, but the results are likely to be only temporary, unless the patient can be tided over until a natural remission occurs.

P. M. F. Bishop
Guy's Hospital, London. R. R. de Mowbray.

FUNCTIONAL DISORDERS AFTER GASTRECTOMY

Sir,—We have read with great interest Mr. Crawford Stanley's letter of May 31.

We did not say that *all* surgeons removed only the major part of a healthy stomach in order to treat a duodenal ulcer. We said: "every time that a surgeon removes the bulk of a healthy stomach . . ." On the Continent this operation is called *Resektion für Ausschaltung.*

With regard to the appearances of so-called hypertrophic gastritis, we are convinced that this state is purely transient, and often associated with portal hypertension. This condition is not curable by removing some of the symptoms by means of gastrectomy. (Note that the hyperchlorhydria and discomfort are really symptomatic of portal hypertension.)

We do earnestly plead for a more objective, and not necessarily a surgical, approach to this growing problem of gastroduodenal ulceration.

David Haler
London, W.1. Kasper Blond.

CONTROLLED HYPOTENSION AND ITS EFFECT ON RENAL FUNCTION

Sir,—We are grateful to Dr. Locket (June 7) for his comments on our paper. We have evidently failed, in the interests of brevity, to stress the more important point, that no serious renal effects followed the use of hexamethonium bromide in our cases. The minor sequelæ with which he is concerned are of doubtful significance.

G. E. Hale Enderby
Queen Victoria Hospital, East Grinstead. Barbara Evans.

Sir,—Whether Dr. Evans and Dr. Enderby (May 24) are correct in their conclusions or not, it would appear that the effect of hypotension on the renal function is irrelevant in assessing the dangers (which are not inconsiderable) of that technique. Dr. Graham Hayward[1] has pointed out that unsuspected coronary disease is becoming increasingly common even in young and apparently healthy people, and that it may be quite symptomless and impossible to diagnose, even by electrocardiography. It is probable that the numerous deaths which have occurred in association with this technique are due to infarction in patients suffering from unsuspected coronary disease. The question of renal damage due to this technique would appear to be of minor importance.

London, W.1. R. Blair Gould.

ANÆSTHESIA IN THE CASUALTY DEPARTMENT

Sir,—I cannot let last week's article by Dr. Rook pass without comment. He describes the technique employed at the Birmingham Accident Hospital and includes 4627 general anæsthetics given in 1950. Though I have no doubt of its efficacy when used at that hospital, equally I have no doubt that very few other hospitals have the facilities that the technique demands—namely, a short-stay ward. This paper is, therefore, not on outpatient anæsthesia, since the cases are converted into temporary inpatients; indeed, the title is misleading since the article describes a modified inpatient anæsthetic technique which is performed for convenience in the casualty department.

Some of Dr. Rook's statements call for particular comment:

"All the patients are premedicated, generally with 'Omnopon' (papaveretum) and hyoscine, in a dose according to age . . . given sixty to seventy-five minutes before operation." This implies that the patient is in hospital for at least 1 hour prior to operation, and for quite some time afterwards. In other words, this technique is quite impracticable at almost every *general* hospital in this country.

". . . thiopentone/nitrous oxide/oxygen . . . the nearest approach to the ideal." With this statement, but not with those that follow as a corollary, I am in agreement.

". . . disadvantages [of the above method] . . . complete recovery may not be very quick. However, the patient is able to regain his reflexes and sometimes consciousness before leaving the theatre." A technique *is* available for the administration of thiopentone/nitrous oxide/oxygen for ambulant outpatients in which anoxia is avoided, good operative conditions obtained, and the patient is always conscious within 1 minute of cessation of the anæsthesia. Moreover, they are able to leave hospital "under their own steam" within half an hour. I am hoping to publish a paper on this technique shortly.

"For longer procedures . . . it has been found desirable to continue the administration of thiopentone by fractional doses." I cannot agree with this statement as applied to the average case. On the contrary, with continued and more complete nitrous-oxide saturation of the tissues (using 20% oxygen) prolonged anæsthesia is usually easy to maintain by inhalation alone. Thus my series includes an anæsthetic of 30 minutes' duration following which the patient regained consciousness in less than 1 minute and was able to leave hospital in 40 minutes.

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[1] Waisman, M., Kepler, E. J. *J. Amer. med. Ass.* 1941, 116, 2004.
[2] Walker, S. A., Rothman, S. *J. invest. Derm.* 1950, 14, 403.
[3] Dillaha, C. J., Rothman, S. *Ibid.* 1952, 18, 5.

[1] Hayward, G. W. *Anæsthesia*, 1952, 7, 67.

With patients liable to vomit "... œsophageal tube is left in situ during induction. Atropine (gr. $^1/_{200}$) is given intravenously before a small dose of thiopentone through the same needle." This dose of atropine is too small, and also, in my experience, intravenous atropine takes at least 5 minutes to act effectively. Unless time is allowed for the drug to act (if a thiopentone-irritability of the larynx is to be suppressed), there is no point at all in its administration.

"No patient who has had a general anæsthetic is allowed to go home alone." It is often quite impracticable, especially in country districts, to obtain somebody to accompany the patient home. In a series of 100 consecutive adult outpatients, and using my thiopentone/nitrous oxide/oxygen technique, 56% left hospital in perfect safety unaccompanied.

Dr. Rook does not state the average length of stay in hospital following general anæsthesia in even minor surgical procedures. I infer that 4 hours is not an unusual time.

Department of Anæsthesia,
Bedford Group of Hospitals. E. HARVEY FRANKS.

VARICOSE ULCERS

SIR,—I have read with interest your annotation of April 5 and the subsequent correspondence.

Practically every case of varicose ulceration is seen by a general practitioner in its early stages. Often the patient is under treatment for varicose eczema; and the practitioner's hope of preventing ulceration will depend on prompt control of œdema.

The technique described here combines all the accepted routine methods, adapted to conditions in the patient's home.

The following explanation is given to the patient, to ensure coöperation:

The skin is a sheet of tissue, drawing its nourishment from the constant *stream of blood entering and leaving it.* If this stream is slowed by back-pressure along the veins, the skin loses vitality and at the same time gets soaked with water from the blood-stream. Just as wet blotting-paper is soft and easily damaged, so swollen wet skin is liable to ulcerate. The aim of treatment is, firstly, to "dry out" the skin, and, secondly, to prevent stagnation and sogginess of the skin.

The patient is never treated in the surgery. He is given a prescription for a roll of 'Viscopaste' and a roll of elastic adhesive bandage and told to go home to bed for three days, during which the affected leg is to be raised on three pillows. On the third day the doctor visits the patient. If the patient has disobeyed the instructions, or if the time has been too short, pressure will elicit pitting. If the slightest œdema persists, the patient is told to rest in bed for a further two days. When the skin is quite "dry," the bandages are applied.

The patient's leg is flexed at the knee; and he is told to point the big toe at his nose, to keep the ankle fully flexed. This flexion obviates the risk of cutting the instep when walking. The viscopaste bandage is applied from toes to knee, leaving no bare patches which might be irritated by the elastic adhesive bandage; this is applied over the viscopaste, leaving no bare patches which might soil stockings and shoes.

The patient is then allowed to get up and go to work. The usual caution is given co[illegible] pain, itching under the bandage, and [illegible] toes.

A workman who cannot afford to stop work is best advised to go to bed on Friday evening or Saturday afternoon, and to stay in bed until Monday morning. A busy housewife with children can do likewise, since the husband will be able to run the household during the weekend. Where this short period fails to achieve complete "drying," bandages can be applied for one week and the process repeated during the next weekend.

With long-standing ulcers in elderly people where the arterial blood-supply is deficient, pressure may be badly tolerated and the bandages must be cut away until the patient is comfortable. Most other patients appreciate the complete sense of support, the regained shapeliness of the leg, and the lack of exudate and of daily bandaging. The bandages can be kept on for months, re-applied when necessary, and finally replaced by crêpe bandages, if the patient can be relied upon to use these properly.

Hornchurch, Essex. I. H. J. BOURNE.

SERUM TESTS FOR SYPHILIS

SIR,—In your issue of June 7, you state that the question of adequate treatment of Wassermann-fast reactors has been complicated by "the employment of cardiolipin as the antigen in the Wassermann reaction; for this increases the sensitivity of the test so that in such cases the reaction remains positive longer."

You might also have questioned whether there is any justification for the continued use of cardiolipin antigen. Pangborn's work was directed to the isolation from beef-heart of the substance reacting with sera from cases of syphilis; and the outcome of this research was cardiolipin, which was inert by itself but serologically active when combined with lecithin and cholesterol. Having isolated a pure substance, Pangborn had to put it back into the complex lecithin-cholesterol mixture in order to produce an antigen. This, from all reports, is more *sensitive but is no more specific than the better-known* serological tests in routine use.

Increased specificity was the aim in the first place; and for this cardiolipin is not the answer.

West of Scotland
Neuro-Psychiatric Research Institute,
Glasgow. D. B. COLQUHOUN.

PARACOLON BACILLUS ENTERITIS

SIR,—Dr. Kernohan's account (May 31) of a case of paracolon bacillus septicæmia prompts me to describe the following confirmed case of paracolon enteritis.

A young married woman, aged 24, was admitted to hospital with a history of sudden onset of severe abdominal pain and uterine hæmorrhage following on six weeks' amenorrhœa. Clinical findings were vague, and ectopic pregnancy was provisionally diagnosed. Expectant treatment was adopted. Her condition did not improve, and after three days a laparotomy was performed; the findings were negative, and the abdomen was closed after appendicectomy.

On the second day after the operation abdominal pain recurred, and on the third day there were several loose motions. Bacteriological examination of the fæces on three successive days showed in each case a predominant growth of a non-lactose-fermenting organism, which was identified as a paracolon bacillus. This organism was agglutinated by the patient's serum to a titre of 1/1000. At the same time a routine Widal agglutination test was negative. The organism was insensitive to sulphonamides and penicillin but very sensitive to streptomycin, chloramphenicol, and aureomycin. Further inquiries into the patient's history revealed that she had had occasional attacks of diarrhœa during the three or four months preceding her admission to hospital.

At this stage it was considered almost certain that the paracolon organism was a true pathogen, and chloramphenicol was administered in a dosage of 0·5 g. six-hourly for twelve days. This treatment quickly caused considerable improvement; but after a few days the diarrhœa recurred, and once again the paracolon bacillus was recovered from four successive cultures of fæces and it was now only slightly sensitive to chloramphenicol. This antibiotic was therefore discontinued, and streptomycin was administered both by mouth (0·5 g. t.d.s.) and intramuscularly (1 g. b.d.) for ten days. This was rapidly followed by complete relief of symptoms. No further paracolon bacilli were isolated from any of three successive samples of fæces. The homologous agglutination titre against the original paracolon bacillus fell to 1/500.

The patient was finally discharged eight weeks after admission. No further symptoms have since appeared.

I wish to express my thanks to Mr. C. R. Macdonald and Dr. F. Hampson for permission to publish this case.

Central Pathological Laboratory,
Grimsby General Hospital. H. LAWY.

ACUTE RENAL FAILURE

SIR,—Your annotation last week affirms that, once nuria has been established, its clinical course is similar hatever its cause; yet you then assert that explanaons according all types of anuria a common pathoenesis are "so vague that they have little significance." his assertion ignores the enormous amount of evidence ollected in favour of the Trueta mechanism or "Oxford hunt." Categorical evidence of the existence of this nechanism under physiological conditions has been roduced by Louvgren,[1] and Kramer et al.[2] have dduced further proof. If Shaw Dunn and Montomery's *original paper of 1941*[3] *is carefully read,* t will be seen that *all* the cases of anuria described howed ischæmic damage to cortical nephrons but the ubcapsular and juxtamedullary nephrons escaped. In 950 Sheehan,[4] in a review of his considerable material, ound an identical pathology, which he divided according o various stages of development. Similar support comes rom Govan and MacGillivray, whilst Solymoss[5] and De and Sengupta[6] have found the same change especially noted in eclampsia). Iversen[7] by kidney iopsy on the eighth day of anuria found the glomeruli loodless, the proximal tubules apparently normal, and heme casts in Henle's tubules.

Many of the dissections on which Oliver[8] reports were performed on Shaw Dunn's original specimens. The conflict of evidence on identical material cannot be reconciled, and reasonable opinion must incline to the view that the over-all pattern of damage as observed on the slide is the true pathological picture. Were it not for this divergence, the Trueta mechanism would explain the tubulorrhexis as resulting from ischæmia.

You say that tubulorrhexis occurs "principally in the distal convoluted tubules or the collecting tubules . . . and can sometimes be found in other parts of the proximal convoluted tubule"; but Oliver emphasises when dealing with its site of incidence (p. 1312) that "the first of these is the *terminal part of the proximal convolution* . . . and the second the distal convolution and collecting tubule." The ischæmic evidence is thus underlined, for its incidence is primarily on highly specialised tissue, whereas secondarily it falls on portions which are less important and at a distance from the supplying vessel. This oversight has further led you into error, for you instance as contradictory evidence the fact that the proximal convoluted tubule is involved and that it necroses when "pure renal ischæmia" is produced in dogs. Should you perforce agree that the site of damage is no longer in dispute, it is not a far step to conclude that the degree of damage—tubulorrhexis or necrosis—will depend on the degree and continuity of the ischæmia provoked. The basis of the Oxford mechanism is a peculiar distribution of renal vascular tone, and this implies a flexibility which crude acute direct renal experiments cannot reproduce. This will affect and vary the critical opening and critical closing pressures in the area involved and also the damage of consequent ischæmia. I believe that this is the process that Oliver unwittingly uncovers when he suggests that "exactly the right degree of ischæmia must be applied to produce tubulorrhexis," and with this explanation there can be no difficulty in accepting the concept of a balanced mechanism underlying "

The Oxford mechanism is

experimental evidence.

The spectacular experiments of Hoff[9] have shown that "lower nephron nephrosis" can be produced via renal ischæmia consequent on stimulation of the frontal area of the cat's brain, provided that the renal nerves are intact. From his illustrations the early and immediate effect is one of cortical ischæmia dependent on glomerular shut-down and accompanied by medullary congestion. This described change cannot be distinguished from the Trueta "shunt." Those who read the article will be convinced that the dilated glomeruli of the late stage of "lower nephron nephrosis" supervene on earlier glomerular shut-down. Further experimental evidence on a small scale, however, was provided by Franklin and Sophian[10] when they succeeded in producing "*lower nephron nephrosis*" (*and cortical necrosis in one case*) by long-continued intermittent electrical stimulation of the renal nerve in rabbits.

Experimental evidence such as this helps to substantiate the findings of the pathologist that diversion of the renal blood-flow of the Oxford pattern is responsible for anuria by a shut-down of glomeruli, which may be absolute or of such extent as to prevent the pressure sufficing for glomerular filtration.

The action of hæmoglobin has been studied by Phillips et al.,[11] who have shown that its injection tends to increase the blood-pressure and to decrease both the glomerular filtration-rate and the renal blood-flow. Such evidence as this is therefore not opposed to the occurrence of renal ischæmia. Their findings coincide with Oliver's, inasmuch as these solutions do not provoke renal damage.

The crux of the matter, however, lies deeper—in the attempt to explain anuria. Apparently you do not question the continuing production of glomerular filtrate and its leaking away through imperfections of the tubule wall. Others ascribe the oliguric tendency to an extreme degree of tubular reabsorption. The former contention is untenable, if blocking casts intervene, between glomerulus and tubulorrhexis areas, without gross tubular dilatation being evident proximal to the cast. Such a change is not found. Additionally, if leakage is occurring, it seems highly unlikely that the tubular detritus would remain localised at the point of solution in continuity, as it is, and that it should not be swept away. The other view can have no support. It is quite unreasonable to believe that damaged and dying structures are capable of exceeding their normal physiological activity. Only one explanation remains—the one I have consistently advanced—that glomerular filtration fails. This is because glomerular spasm is of such an extent as to prevent glomerular pressure reaching adequate filtration levels.

Biochemists are gradually conceding greater importance to glomerular filtration vis-à-vis tubular function. Lauson[12] states that in normal subjects the urine flow per 100 ml. of glomerular filtrate and its inverse the urine/plasma inulin ratio are determined inter alia by the rate of glomerular filtration. This emphasises that a reduced glomerular rate is a determinant of the amount of urine secreted.

But Bykov's[13] experiments on conditioned antidiuresis in dogs carry the matter much further. He has adduced evidence to show that the glomerulus can function as the leader of the renal orchestra on whom all depends. For in ring-hypophysectomised dogs (diabetes insipidus) he has elicited conditioned antidiuresis, conclusively showing that urine secretion can be brought under absolute glomerular control in the complete absence of antidiuretic hormone. There is one proviso—that the renal innervation is intact. This pathway obviously permits of glomerular control by the higher centres. Can such a stimulus be excluded in anuria or even during physiological activity?

I am of the opinion that it cannot and that it must intervene in all our assessments of renal function. The

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1. Cited by K. J. Franklin at the International Conference on Circulation, Ciba Institute, 1951; also personal communication.
2. Kramer, K., Saxon, G. A., Timmons, D. E. XVIIIth International Physiological Congress, 1950; p. 52.
3. Shaw Dunn, J., Montgomery, G. L. *J. Path. Bact.* 1941, 52.
4. Sheehan, H. *Proc. R. Soc. Med.* 1951, 44, 399 (not fully reported).
5. Solymoss, A. *Lancet*, 1949, i, 957.
6. De, S. N., Sengupta, K. P. *Ibid*, 1951, ii, 1100.
7. Iversen, P., Brun, C. *Amer. J. Med.* 1951, 11, 324.
8. Oliver, J., Macdowell, M., Tracy, A. *J. clin. Invest.* 1951, 30, 1305.
9. Hoff, E. C., Kell, J. F. jun., Hastings, N., Sholes, D. M., Gray, E. H. *J. Neurophysiol.* 1951, 14, 317.
10. Franklin, K. J., Sophian, G. J. *Proc. R. Soc. Med.* 1951, 44, 401.
11. Phillips, R. A., Killough, J. H., Gilder, R., Smith, R. L. XVIIIth International Physiological Congress, 1950; p. 395.
12. Lauson, H. D. *Amer. J. Med.* 1951, 11, 135.
13. Bykov, K. M., 1947 (Russian translation).

Trueta "shunt" is its expression. All anuric stimuli eventually react on the "neurility" of the kidney (De Muylder)[14] provoking diversion of the renal blood-flow. Chemical poisons acting as anuric stimuli are first perceived by the proximal convoluted tubule. Once the noxious substance has filtered through the glomerulus it becomes absorbed by this portion of the nephron which it damages (nephrotoxic changes of Oliver), and simultaneously evokes renal blood-flow diversion to protect the more vulnerable and more important nephrons of the cortex.

The diversion of the renal blood-flow has a physiological purpose. At its initiation it can protect the kidney, as in the above instance. Similarly it can aid the organism as a whole by diverting a large portion of the renal blood-flow into the general circulation when this is depleted after hæmorrhage, or when this is inefficient as in shock or cardiac failure. When large amounts of extracellular fluid are out of circulation, as in crush injury, the kidney may mistakenly respond with a shut-down that is meant to be protective. Anoxia can similarly evoke such a reaction Increased tension of the uterine wall, possibly reducing placental circulation, does provide a physiological stimulus also.

It is the province of the clinician to determine at what stage this pervading protective mechanism is both valueless and menacing; imperatively also to determine what therapeutic measures can suffice against it. But to this end the first need is to unravel its basic pathology (physiology ?); and your annotation has provided a further stimulus.

London, W.1. JOHN SOPHIAN.

SIR,—Your annotation last week serves a useful purpose in drawing attention to the paper by Oliver and his team[15] on the microdissection findings in renal tubular necrosis—work which justifies a completely new view of the pathology of the condition. It is scarcely possible in a short editorial to do justice to a detailed article of 40 pages; but in one respect your annotation seems actually to be misleading. You state that "the common type of tubulorrhexis affects the 'lower nephron.'" Leaving aside the ambiguity of the phrase "lower nephron," the selective involvement of the distal nephron, crystallised in the term "lower nephron nephrosis," has been conspicuously absent from Oliver's material, of which he himself says (p. 1326): "This lesion [tubulorrhexis] occurs in all parts of nephron indiscriminately from the proximal convolution to the collecting tubule." Since necrosis of the tubular epithelium without rupture is confined to the proximal tubule, there would seem little justification for retaining the term "lower nephron nephrosis," to which the term "acute tubular necrosis," used by Bull, Jockes, and Lowe[16] is much to be preferred.

In patients who have died 10–15 days after the onset of acute renal failure, ordinary histological examination of the kidneys reveals an impressive amount of new growth of tubule epithelium; and this has been taken to mean that if the patients can be tided over a critical period, all will be well. Oliver's dissections of nephrons in continuity show that this tubular regeneration may be a vain thing, in that it fails to restore a tubular lumen; and he holds that tubulorrhexis means the end of the nephron involved. Survival depends on the recovery of less damaged tubules, whose inaction has been due to temporary circulatory disturbance. This concept of Oliver's explains rather well the tendency of these patients to become stabilised at an adequate, but definitely subnormal, level of renal function.[17] This new work does not detract in any way from the imp rta servative management of acute renal perhaps emphasises the need for cauti in cedures such as "controlled" hypoter in which must induce renal ischæmia.

Department of Medicine,
University of Manchester. D. A. K

ACUTE SORE THROAT

SIR,—Dr. Bishop and his colleagues, in their p week, give statistics to prove what the maj general practitioners have known for years— that penicillin is the treatment of choice f bacterial throat infections. I would, howeve their contention that the use of sulphadim unjustifiable; this drug will nearly always cure cases which do not respond to penicillin. This illustrated by a case which came under my care

The infection presented as a typical follicular t but after 48 hours' treatment with penicillin, there improvement. Culture of a throat swab yielded growth of *Bact. coli*; and on substituting sulpha there was a prompt fall in temperature and am symptoms and signs. The alternative would have use one of the expensive new antibiotics.

There must be very little, if any, evidence effects of any consequence resulting from the sulphadimidine in therapeutic doses.

Twickenham, Middlesex. DAVID WH

PROVISION FOR THE MENTALLY DEF

SIR,—In your annotation last week you recommendation for a more courageous policy of the release of high-grade patients from in What is the courage that is urged ?

To be found mistakenly optimistic so that patient fails, to invite criticism from hospital ma committee or higher authority for the results failure, to attract censure for raising the c licensing the useful workers—these are risks w have the courage to take. But to harm a pat licensing him before he is ready, so that his fail him back, *to risk the feelings or the safety of a* wo child who may be frightened or molested by patient, *to risk the production of a fatherless* an less child by an unwisely licensed female patient are risks for which others pay. They are not t acts of courage but as acts of ill-judgment, weak the face of pressure, neglect of the public good.

We who have the responsibility of giving licen recommending full discharge must take the form of risk. We must not be bullied or cajoled into th by critics who know little of the facts and will be of the burden of mistakes.

St. Albans, Hertfordshire. NOEL H. M. BU

APPOINTMENT SYSTEMS IN HOSPITA OUTPATIENT DEPARTMENTS

SIR,—Brigadier Welch and Mr. Bailey (May to be congratulated on their careful and dispas approach to a very important subject. They m special reference to teaching hospitals, but it w interesting to know whether they had conside special difficulties of outpatient appointment syst such institutions. In order to assemble mate teaching purposes, it is necessar voir of cases at the beginning of inevitably mean a long waiting-time for some p not selected for teaching. I have so far failed to fi solution of this difficulty.

London, W.1. E. STANLEY

SIR,—I imagine many readers of THE LANCET as I do, as much interest from the correspondence follows a provoking article as from the article its

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14. De Muylder, C. G. The Neurility of the Kidney. Oxford, 1952.
15. Oliver, J., MacDowell, M., Tracy, A. *J. clin. Invest.* 1951, 30, 1305.
16. Bull, G. M., Jockes, A. M., Lowe, K. G. *Clin. Sci.* 1950, 9, 379.
17. Lowe, K. G. *Lancet*, May 31, 1952, p. 1086.

g the article by Brigadier Welch and correctly forecast to myself that there rather snappy response with little, if any, of consultant unpunctuality. Everyone well those circumstances in which lateness ided. However, after eight years' experi- r in hospitals, I would like to mention two (1) some consultants are late *by habit* er reason; and (2) the busiest consultants e their lives so that punctuality is possible e day.

t print my name as I should always have myself.

PRACTITIONER.

the *Medical Directory* writes: "The accuracy depends on the return of the annual schedule, posted to members of the medical profession. edule have been mislaid I will gladly forward n request. The full name of the doctor should ntification." The directory is published by Churchill Ltd., 104, Gloucester Place, London,

Parliament

Hospital for Tropical Diseases

House of Commons on June 10, Colonel J. H. drew attention to the facilities offered at the Tropical Diseases, which a year ago moved nt building in St. Pancras Way, London. He pital now had 68 beds, an outpatient clinic, laboratories, and lecture-rooms for post- dents. He was anxious that men discharged East, and private citizens who had come country suffering from tropical diseases, the benefit of treatment there. But it was some patients to travel to London, and son suggested that periodically one of the from the hospital should visit provincial

ICIA HORNSBY-SMITH, Parliamentary Secre- Ministry of Health, said that her department Ministry of Pensions were anxious that the the Hospital for Tropical Diseases should be Servicemen and pensioners. But there was, no evidence of an unusual prevalence of ases in this country. The value of the recognised by the Ministry, and they were s world-wide reputation. It was always t the hospital should be a consultative centre sed treatment in tropical diseases. The hospital medical staffs and the senior adminis- cal officers of all the regional boards had been to the work of the hospital; and any general could send a patient direct to the hospital, there was a comparatively short waiting-list for treatment. It was not easy to send specialists t, but she would certainly see if there was any e of particular need in certain areas.

Third Readings

he House of Lords on June 12 the Agriculture ous Substances) Bill and the Corneal Grafting re read the third time.

QUESTION TIME

Savings from Prescription Charges

ying to Major TUFTON BEAMISH, Mr. IAIN MACLEOD, nister of Health, said that the estimated savings l year from the charges authorised by the National Service Acts of 1949, 1951, and 1952 were £12 million, lion, and £7 million, giving a total of £44 million.

MICHAEL STEWART asked the Minister of Health tion he had advised hospitals to take in the case of nts who, in urgent need of medicine prescribed for were required to pay the prescription fee, and had ey with them for this purpose.—Mr. MACLEOD replied: ntent to rely on the discretion of hospital authorities in this rare combination of circumstances. Mr. STEWART: Is the Minister aware that hospitals are already faced with this problem and that some hospital boards are at a loss for a solution? Mr. MACLEOD: I have been round the hospitals since the appointed day and I have not found these difficulties.

Mr. ANEURIN BEVAN: Does the Minister mean that the hospitals have discretion to waive this charge? Mr. MACLEOD: If the sort of circumstances mentioned arise in which an outpatient urgently needs medicine and cannot pay the shilling charge, and has no time to apply to the Assistance Board for it, I am content to rely on the discretion of the hospitals.

Changes in Names of Hospitals

Mr. R. T. PAGET asked the Minister of Health whether he would alter the name of the Royal Cancer Hospital and of any other hospitals under his control whose names had an alarming effect on patients.—Mr. MACLEOD replied: I am prepared to consider any proposal for a change of name put forward by the board of governors of this or any other teaching hospital. Regional hospital boards may, in consultation with the management committees concerned, make such changes in the names of non-teaching hospitals as they think fit.

Mr. PAGET: Could the Minister suggest to the Board of the Royal Cancer Hospital that such a change might be desirable? Mr. MACLEOD: Yes and no. The initiative rests, so far as teaching hospitals are concerned, very properly with them, but it is true that the board of governors are considering this matter at the moment, and it is probable that a formal approach will be made to the Ministry of Health.

Rayon Surgical Dressings

Mr. T. E. N. DRIBERG asked the Minister of Health what tests had been carried out in the use of rayon in surgical dressings, and with what result.—Mr. MACLEOD replied: The use of rayon in elastic adhesive dressings, elastic bandages, and cotton crêpe bandages is already authorised. Following satisfactory tests the supply of rayon lint against medical prescription will shortly be approved. Clinical tests of rayon surgical gauze and rayon bandages are still in progress.

Proprietary Pharmaceutical Products

Dr. A. D. D. BROUGHTON asked the Minister of Health if he would introduce legislation to make it compulsory for pharmaceutical firms to state the price of their products when advertising drugs and medicines to medical practitioners.—Mr. MACLEOD replied: While I agree that it is most desirable that doctors in the National Health Service should know these prices, I am not yet clear that the imposing of a requirement to state them in advertisements is a suitable subject for legislation, but I should like to think further about the matter.

In a further question Dr. BROUGHTON asked whether the Minister would instruct executive councils to compare the average cost of each doctor's prescriptions with the average cost over the country as a whole, and whether this matter would be watched at least as carefully as it was under the National Health Insurance scheme. Mr. MACLEOD: The great difficulty is that pricing itself is ten months in arrear. We are trying to get on as fast as we can with the idea which the hon. Member has in mind.

Food Protection By-laws

Replying to a question, Major GWILLYM LLOYD GEORGE, Minister of Food, said that 1263 local authorities in England and Wales had made by-laws under the Food and Drugs Act, 1938, for the protection of food while on sale in shops or during the course of delivery. The by-laws were enforced by the local authority, and the Ministry of Food had no statutory authority in the matter.

Shared Telephone Lines

Mr. IAN HARVEY asked the Assistant Postmaster-General to what extent doctors were required to share a telephone line.—Mr. L. D. GAMMANS replied: A doctor is always given exclusive service to his surgery and the line is charged at the business rate; this applies also where his surgery and residence are in the same premises and are served by one line. Since Jan. 1, 1948, all doctors have been under obligation to share their telephone lines to their private houses if they do not practise there. In such cases the line is charged at the residence rate,

Notes and News

THE MEDICAL ILLUSTRATOR

MEDICAL illustration presents its exponents—whether artists or photographers—with some remarkable and exciting technical problems. The beautifully arranged exhibition, "Photography and Art in Medicine," on view at British Medical Association House until June 28, and to be shown again at Manchester University on July 5–19, contains works intended for the teaching of students, and for display in museums, as well as a few recordng the features of some striking case.

The anatomical drawings, in the "art" section, are exquisitely precise. Coloured drawings of lesions seem to have every possible advantage over photographs until the examples of colour photography offer them a direct challenge. Both have their place, however, for where something more than direct representation is needed the human mind can still achieve more than the camera. Thus Audrey J. Arnott, illustrating a case of fracture of the petrous bone, is able to indicate the course of the escaping cerebrospinal fluid through the mastoid and middle ear into the eustachian tube. In such a case the eye of the artist looks imaginatively through the skull, and draws what even X rays could not show. On the other hand, the photographer can present the texture of a lesion in monochrome and set this alongside a transparent colour-photograph for comparison. Several such paired photographs appear in the "transparencies" section, and are extremely informative. Photographs are also effective for showing the stages in a case-history. An emaciated infant with Hirschsprung's disease converted by recto-sigmoidectomy into a stout and cheerful one, and a premature baby in an incubator blowing up like a balloon to normal dimensions, make two memorable series. Again, photography shows microscopic cell changes far more credibly than any drawing could. F. E. Speed's photomicrographs of normal mitosis in a chick fibroblast, and mitosis in a rat kidney treated with styryl aminopyrimidine, are quite outstanding. Moving pictures, too, are extremely successful in this field. A film showing mitosis of a chick-embryo fibroblast in tissue culture, speeded up a hundred times, is shown by the new method of rear projection. Here a projector is used in conjunction with a television screen, and since the image is brilliant, the film can be watched in daylight—a useful point for the teacher, who is thus able to keep not only the projector but the class under his direct control.

When it comes to skin lesions neither ordinary art nor photographic artifice is entirely satisfactory; and here waxworks take the field. Alice Gretener presents some disturbingly life-like wax models of ulcers, burns, skin diseases, and cancer, as well as a wax model of a congenitally deformed heart mounted in a 'Perspex' container.

One branch of medical illustration—and that more familiar to doctors, perhaps, than any other kind—is not represented at all in this exhibition. Medical journals and textbooks are commonly illustrated with diagrams and graphs which are very carefully prepared for their purpose, and which require not only good draughtsmanship but also a thorough knowledge of lettering and what is likely to befall it when it is reduced on the page. Illustrators who are inexperienced in this work seldom get the lettering right; they remember that some main statement will be reduced, and give it proper emphasis, but they often overlook the necessity for giving appropriate weight to the figures or lettering of less importance. This bit of technical knowledge and skill is so important to both publishers and readers that we wish it might be given a place, however inconspicuous, in future exhibitions.

It is perhaps noteworthy that in this exhibition the exhibitors in the art section are mainly women, while the photographic exhibitors are mainly men. Does this reveal a sex-determined difference in taste or opportunity, or both?

Royal College of Obstetricians and Gynæcologists

The council of the college offers two Leverhulme scholarships of £500 a year each, renewable for a second and third year, for the purpose of research into problems connected with obstetrics and/or gynæcology. Further information may be had from the secretary of the college, 58, Queen Anne street,

University of Oxford

On March 11 the degree of D.M. was conferred
Poulton and of B.M. on A. N. Cammock (in absentia

University of Cambridge

On June 5 the honorary degree of SC.D. was con
Sir Gordon Gordon-Taylor, consulting surgeon to t
Navy and to the Middlesex Hospital. Mr. W. K. C
the Orator, described Sir Gordon as "chirur
secundus," a pioneer in "arte sanguinis in vena
transfundendi," who when he took pen in hand
"summam lectori iucunditatem et delectationem."

On June 7 the following degrees were conferred:

M.D.—J. O. P. Edgcumbe, R. H. Wilkinson.

University of London

Dr. C. F. Barwell has been appointed to the Go
Company's chair of bacteriology at the London
Medical College from Oct. 1.

Dr. Barwell, who studied medicine at the University of
Afte
at th
.S. p
teriol
I papers on chronic m
c virus, and on the
c phogranuloma vene

University of Birmingham

The council will recommend to the court of
that Prof. H. F. Humphreys, M.B., M.D.S., vice-pr
the university and professor of dental surgery, be
vice-chancellor and principal for the year beginnin
1952. Prof. A. P. Thomson, F.R.C.P., dean of th
of medicine, has been appointed to succeed
Humphreys as vice-principal.

Royal College of Surgeons of England

At a meeting of the council held on June 12, with
Wakeley, the president, in the chair, Mr. Geoffre
was appointed honorary librarian of the college. The
were coöpted to the council for 1952–53 representin
branches of practice:

Prof. A. M. Claye (gynæcology and obstetrics), Mr. M.
(otolaryngology), Mr. J. H. Doggart (ophthalmology), S
Kelsey Fry (dental surgery), Prof. B. W. Windeyer (ra

Prof. Matthew Stewart and Prof. Geoffrey Hadf
appointed Imperial Cancer Research Fund lecturers.

Mr. F. McGuckin, Newcastle upon Tyne, was e
the fellowship *ad eundem*. Diplomas of fellowship wer
to the following:

A. J. Abraham, L. C. Robson, S. F. Hans, J. R. Br
Littler, D. B. Griffiths, K. L. Wilson, C. D'A. Laidlaw, E.
K. H. Smith, S. P. W. Street, R. C. Farrow, J. E. Holg
Sage, J. O. Robinson, J. T. Row
I. Westc
W. B.
Michae
C. Mustarde, R. A. Burn,
Sivagnanam, Padma Pral
n Thompson, Martin Horv
Ranking, Syed Ashfaq Ha
lsom, Dorothy M. Ridout,
Wetherell, Ghali Abadi
L. W. Godfrey, Richard Harrison, Ramesh Kumar, R
Megally, A. H. Moore, I. M.
M. K. Smith, G. S. Tupman,
Hormasji Antia, L. C. Bell, Be
Dickson, A. P. M. Forrest, P.
Kaikhushro
L. S. Symon
Percy Helm
Shukri, R.
Rao, B. F.
Rajasinghe
Ian Ranger
Sherrah-Da
Holland.
R. T. Newham, Aziz
xman Vaze, Pulaker
L. Kermond, G.
J. A. O'Brien, Don
Schlicht, F. K. Sh
I. Hall, D. G. Tayl

A diploma of membership was granted to J. G. Woth
The following diplomas were granted jointly with t
College of Physicians:

D.M.R.-D.—F. G. Anderson, W. E. C. Astle, Raghuba
Alan Bryce, D. C. R. Burrows, A. C. E. Cole, Phyllis A.
I. J. Geere, I. R. S. Gordon, J.
Yew Lien, Bridget P
indra Nath Sen, Mor
Har Bhajan Singh, Philippa M. Southey, Basil S
Chai-Hee Tsao, Eric Walker, J. K. Walker, I. P. William
Wray.

D.M.R.-T.—John Beech, Bronislaw Chudecki, Mary
J. P. Concannon, M. L. Dyson, M. J. Garrett, J. S. Lo
McArthur, *Jean Michon*, K. A. Newton, R. C. S. Point
Thomson, Sistla Venkateswarlu.